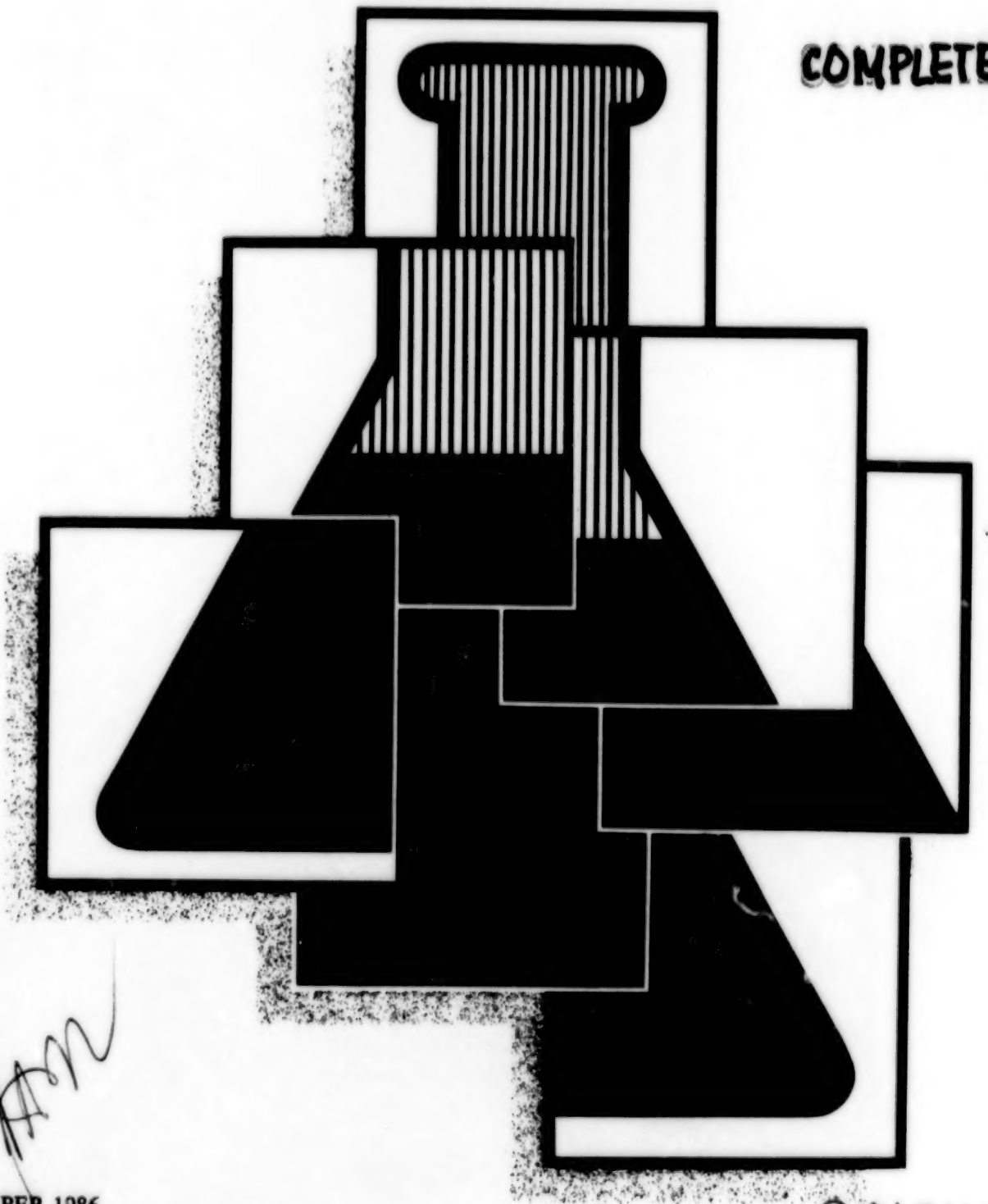
U.S. Department of Justice
Drug Enforcement Administration
Office of Diversion Control

Proceedings of Controlled Substance Analog Leadership Conference



DECEMBER 1986

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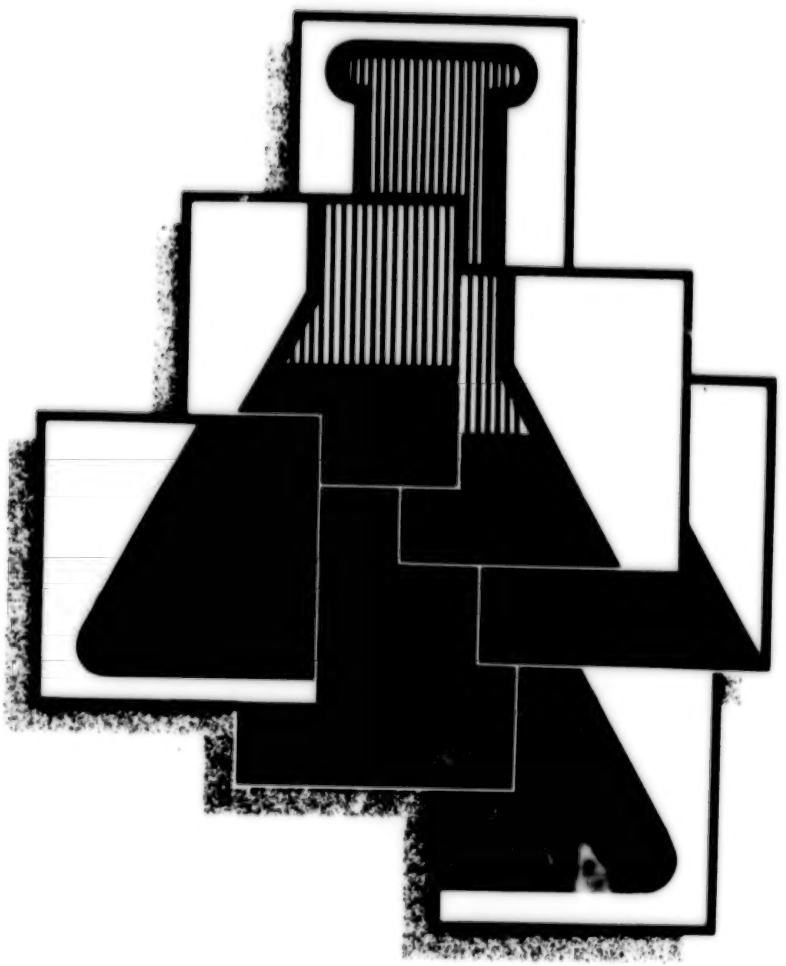

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PREFACE

Over the past several years, the clandestine manufacture, distribution and abuse of controlled substance analogs has presented yet another unique challenge to those fighting drug abuse. Referred to as "designer drugs" in the media, these substances produce the effects of controlled substances such as heroin, LSD and amphetamine, but because they differ slightly in chemical structure from controlled substances they are not regulated under the Controlled Substances Act. As soon as one of the analogs is controlled under the Controlled Substances Act, another substance with a slightly different chemical structure is produced to take its place. Hence, individuals have reaped huge profits from the manufacture and sale of these highly abusable substances without the fear of being prosecuted under existing drug laws.

The concept of producing pharmacologically similar chemical variants of controlled substances in a deliberate attempt to evade the law is not new. Analogs of amphetamine and mescaline such as MDA, DMA, TMA, DOM and DOB, were synthesized and abused in the 1960's and 1970's. Analogs of the hallucinogen phencyclidine (PCP) and the depressant methaqualone were also synthesized in the clandestine laboratories of the 1970's. It was not until the 1980's, however, that we witnessed the clandestine production of totally synthetic, extremely potent narcotic substitutes for heroin. The controlled substance analogs of recent years include analogs of the narcotic analgesics fentanyl (Sublimaze) and meperidine (Demerol) and analogs of the stimulant/hallucinogenic phenethylamines and phenylisopropylamines.

The controlled substance analog phenomenon has created special problems for everyone associated with the drug abuse situation, from the user to medical personnel, law enforcement officials, chemists, educators and public administrators. The high potency, unknown or toxic effects and unregulated syntheses of many of these analogs have posed serious health risks to those exposed. Fentanyl analogs such as 3-methylfentanyl which is up to 5500 times more potent than morphine, have been associated with more than 100 overdose deaths in California since 1980. 1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), a by-product in the uncontrolled synthesis of the meperidine analog, 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP), destroys cells in the brain and produces an irreversible Parkinsonian-like syndrome. MDA and MDMA, both phenylisopropylamines available in the illicit drug traffic, have been shown to produce long-term neurochemical depletions and to destroy nerve fibers in the brains of experimental animals. The actual neurotoxicity of these substances in humans has not been established but the threat to the many thousands of individuals using these substances is real.

In many instances these analogs have not been synthesized by legitimate chemists prior to their clandestine production. Thus chemists have no reference standards or analytical data to help identify the new analogs. Furthermore, some of the analogs produce their pharmacological effects following administration of only minute amounts, adding to the difficulties of the forensic chemist and toxicologist in establishing the identity of the substance. Because of the problems in detecting and identifying the analogs, the true scope and quantitative measure of

their availability are unknown.

Controlled substance analogs can be made inexpensively from readily available chemicals and equipment. Their manufacture and distribution can generate huge illicit profits and they offer an alternative source of abusable and addictive drugs for the drug dealer. Yet law enforcement personnel and the judicial system do not have the requisite legal tools to apprehend and prosecute those who flout existing laws by manufacturing and distributing these dangerous substances. A scarcity of information regarding both the individual substances and the analog problem as a whole hampers those who are charged with educating either professionals or the public regarding these drugs of abuse. Nevertheless, there is a clamor for a solution to the controlled substance analog problem.

In response to these concerns, the Office of Diversion Control of the Drug Enforcement Administration convened a three day multidisciplinary conference of experts to examine the problem, exchange knowledge and recommend solutions. It was held in San Francisco, California on June 9,10, and 11, 1986. The conference focused on the health risks attendant to exposure to controlled substance analogs, problems in identifying and detecting analogs, problems encountered by law enforcement personnel and legislative and educational approaches. Representatives from various federal and state government agencies, experts from medical and scientific institutions and relevant industry representatives shared information and exchanged views on various aspects of the analog problem. Representatives from the World Health Organization and the Canadian government also participated. The first two days of the conference were devoted to papers regarding controlled substance analogs. Topics ranged from the neurotoxicity of MPTP and amphetamine-like compounds to legislative initiatives at the state level. The third day of the conference consisted of round table discussions of the four main areas of concern: 1) health risks and epidemiology, 2) identification and detection, 3) law enforcement and 4) legal aspects. These discussions formed the basis of the recommendations which each group formulated.

This volume contains the papers presented at the Controlled Substance Analog Leadership Conference as well as the recommendations of the expert groups.

It is hoped that the information contained in this volume will aid in the understanding of the controlled substance analog phenomenon and provide a starting point for those agencies and governments that must address this problem.

Special thanks are given to Ms. Debra Lesesne for her countless hours at the word processor and Ms. Carole Whalen and Ms. Gayle Rupert for their assistance with the administrative details of the conference.

Allen C. Church
Frank L. Sapienza

THE "DESIGNER DRUGS"; AN INTRODUCTION TO THE PROBLEM
(Abstract of the Opening Address)

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In the fall of 1978 the Drug Enforcement Administration conducted a review of the Controlled Substances Act, with a view to strengthening the Government's ability to deal with the problem of diverted legal drugs. As a result, a number of deficiencies were identified and new legislation was drafted to deal with them. One of the issues which received brief attention was a proposal for an emergency power to place new drugs of abuse under control by means of a special abbreviated procedure. The process which Congress had originally designed for this purpose had proven to be lengthy and complex and, therefore, unsuited to circumstances in which a public safety problem arising from the traffic and abuse of an uncontrolled substance was rapidly developing. The process could require from several months to several years for completion during which time manufacture and distribution of a drug could proceed in a legally ambiguous fashion. There had occurred at least two circumstances in which existing procedure had been found to be unsatisfactory; the scheduling of methaqualone in 1973 and of alpha-methylfentanyl (China White) in 1981.

Thereafter, relatively little attention was given to the issue except as necessary from time to time to justify the proposal to higher authority. It was not regarded as a major provision of the bill. During 1983 and 1984, two House Subcommittees held extensive hearings on the proposed legislation. Some further attention was given to the "emergency control" provision by the Judiciary Subcommittee on Narcotics because of a problem which was then becoming known as the "designer drug" phenomenon. The term had been coined in California to refer to the clandestine manufacture of analogs of controlled substances such as "China White." It was agreed by both the Committee and DEA that this power should be used to deal with just such situations. Still, few foresaw the events of the coming year. In October of 1984 the Omnibus Crime Bill became law. There were no plans in DEA for the immediate exercise of the new emergency control power; but this relatively obscure provision was soon to become the focus of national attention. The reasons for employing the power were particular to each circumstance, but the fact remains that it was to be used on five separate occasions in connection with 13 different drugs within an 11-month period. What had happened?

The problem of the clandestine manufacture of controlled substance analogs or "designer drugs," as they are called in the media, represents yet another of the bizarre circumstances which are unique to this century by virtue of the massive

growth of scientific and technological capacity. Until the present century the drugs available for medical practice or abuse were principally crude vegetable preparations of relatively low potency. Among the narcotics these consisted of various tinctures and solid forms of opium containing small quantities of natural morphine and related alkaloids. In 1806, morphine was isolated and beginning with the middle of the 19th century the rise of truly potent narcotic drugs gradually spread throughout the medical world. Subsequently, in 1898, Dr. Bayer of Germany reacted morphine with acetic anhydride to produce heroin. The process of moving from agriculture and harvest to laboratory syntheses and high yield continued into the first half of the present century with the development of a range of powerful, totally synthetic drugs. In each case and in each phase of development society recognized the need for control over the production, distribution, and use of these drugs and listed them each in turn within the categories of control.

From a legal point of view this policy was successful because availability from either legal or illicit sources did not outstrip the making of such lists. Traditionally, such lists had been made and added to by acts of Congress, but in the decade of the 1960's it was recognized that events could move too rapidly for such a process and would involve technical judgements best left to administration. Prior to this time it was not uncommon for synthetic drugs to be found in the illicit traffic, but with the exception of heroin, not the actual means of their synthesis. The nationwide development of clandestine laboratories for the manufacture of LSD, methamphetamine, methaqualone and PCP in the 1960's showed that both the knowledge and the means had suddenly become widely and economically available. It was recognition of this change which led Congress to provide a means of adding to the lists administratively in the first place. As previously noted, experience subsequently revealed that even the administrative process could be too slow. The prospect of such rapid change gave rise to the need for emergency control powers.

The Advent of Designer Drugs

A fundamental change had occurred in the level of scientific knowledge and capacity; a change which only slowly became understood by administrators and policymakers - the classic pattern of the century. The level of knowledge in chemistry had advanced to the point where basic molecules of a given design could be produced and modified in a seemingly endless array of possibilities. Moreover, not only the knowledge but the technology and the raw materials were widely available throughout the society. It was becoming possible for any university graduate to "design" the molecule one wanted, to make numerous variations on selected patterns and to research these variations for precise effects desired, i.e., in the parlance of the 1980's to make "designer drugs." Many were interested in such possibilities for the development of new drugs tailored to specific medical needs. Some were interested because of the new possibilities of illicit profit. This development, in both licit and illicit activity, has resulted in extraordinary risk and injury to the abusing population and unprecedented problems in legal and social control. The "designer drugs" phenomena is perhaps the most startling example of these difficulties.

SPECIAL RISKS

Lack of Research

During the 20th century the pursuit of new drugs became a major global

industry. The molecular possibilities, natural or synthetic, were researched according to the prevailing ethical and scientific standards for the discovery of new, useful, and sometimes life-saving therapies. The technology of mass production could then bring the medications within reach of a large part of the human population at a modest cost resulting, nevertheless, in huge profits as well as great advances in health care. The abuse and traffic in such drugs was and is an unwanted side-effect involving only those drugs which also produce certain psychic effects.

For this reason, until quite recently, very little research was done on the effects of the abuse of these drugs. The developers and marketers have only been concerned with licit activity and utilization for medical purposes. Their researches have been largely confined to effects involved within these parameters which is all that is required by law. For this reason much of the scientific data concerning drugs of abuse is of questionable utility in predicting outcomes related to abuse. This kind of "research" is mostly conducted in the street with the results only becoming apparent to the medical and scientific community gradually through the identification of injuries to users.

This particular problem is further exacerbated in the case of so-called "designer drugs," which, being analogs of other drugs, have seldom been researched in any context. Thus, the informal street research is the only research, and the human abusers are the first and only test animals. In such a context many deaths and disasters could be anticipated and have in fact occurred. Perhaps the most bizarre of these is the rash of injuries which have been associated with MPTP, an impurity of MPPP, an analog of meperidine. Here it appears that an unknown number of persons have suffered irreversible brain damage resulting in a "Parkinson-like" syndrome leaving them permanently and severely crippled.

Potency

Another special danger is due to the extreme potency of some of the analogs involved. This is particularly so in the case of analogs of fentanyl which may be several thousand times more potent than morphine. For some of these, a ten-microgram dose--a mere speck on the fingertip--may produce respiratory depression and death. Thus, the risks arising from the imprecise and informal dosage calculations of the illicit trafficker are greatly magnified. Also, the extreme potency of these analogs means that only minute quantities are necessary to produce a desired effect. When coupled with the lack of analytical data and quite general lack of knowledge concerning them, their potency leads to special difficulties in determining the presence or nature of analogs in tissue samples or acquired evidence. Few laboratories, coroner's offices or hospitals have been sensitive to this possibility in their daily activities.

Legal Inadequacy

When all of these problems are viewed together, it becomes clear that present drug control laws are also inadequate. Those seeking to profiteer on these circumstances can synthesize one of the many analogs not specifically listed as under control. Even though there is now a basis at the Federal level for emergency control, one must assume that some period of months would elapse before the problem was identified and prepared for a decision. During this interval tens or hundreds of millions of dosage units could be cheaply manufactured and distributed with

unknown health consequences--all without serious risk of prosecution. Thus, when the phenomenom is viewed in terms of the existing medical, social and legal apparatus developed to deal with such problems, we see serious deficiencies; and although there are parallels in past experience, there are aspects of novelty as well.

At present, the measures taken by Government to control these new compounds on an emergency basis, the development of successful criminal investigations, and the wide publicity of ill-effects have acted to contain the spread of "designer drugs." However, the potential for spread and the possibilities for injury are still enormous. For this reason, the DEA undertook to organize this Leadership Conference on Controlled Substance Analogs in order to bring together experts from all of the areas of concern--medical and scientific, laboratory analyses, public awareness, law, and law enforcement.

The purpose of their deliberations as reflected in this report was first, to provide guidance and recommendations in eac.. area of activity for the benefit of all concerned government and social authorities and second, to increase the expertise of all participants by exposing them to the views of the other disciplines involved. In addition, in view of the interest expressed by our many foreign colleagues it was felt proper to invite the participation of the World Health Organization. All this in some measure, at least as a beginning, has been achieved.

REMARKS

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I welcome the initiative taken by the United States Drug Enforcement Administration to call this multidisciplinary meeting to find solutions for the "Designer Drug" problem. Health workers and law enforcement officials need to collaborate and cooperate in reducing the problems created by those who make money from other people's sickness, disease and death.

The role of the Drug Enforcement Administration in this area has been laudatory and the World Health Organization is grateful for the continued support of DEA in its work. In April 1987 the Expert Committee on Drug Dependence will meet and the topic of controlled substance analogs will be on the agenda. I hope that the results of this conference can provide the World Health Organization with some guidance in its attempt to deal with the problem. The Controlled Substance Analog Conference is very much needed and should be only the first in a series of such meetings at both national and international levels.

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Health Risks & Epidemiology

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THE HAZARDS AND CONSEQUENCES OF THE DESIGNER DRUG PHENOMENON: AN INITIAL APPROACH TO THE PROBLEM

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Introduction

In the last few years it has become apparent that an abundance of new products are brewing in the laboratories of illicit chemists throughout the country. These substances have been referred to as "designer drugs," a term originally coined by Dr. Gary Henderson of the University of California at Davis to denote the increasing ability of underground chemists to tailor, or design, drugs to a client's personal taste (going so far as to specify the color, type of high, potency, and duration of effect). However, the term has now been extended to include a new and much more dangerous phenomenon. During the last six years (and probably longer) these illicit chemists have been actually "redesigning" the molecular structure of well-known (and controlled) substances in order to escape the law. It is possible to make and sell these drugs legally because current drug enforcement legislation requires that any controlled substance be designated specifically by name and structure, and these new, altered compounds (now referred to as controlled substance analogs, CSAs) are therefore no longer controlled. At first glance, an obvious solution would be to control whole classes or categories of drugs. Unfortunately, such a step could put unacceptable restrictions on medical research and legitimate development of new drugs in the pharmaceutical industry.

What are the dangers of these new "synthetic" drugs of abuse? What can be done to stop their proliferation? The purpose of this article is to examine these questions with an eye toward developing a program to deal with this problem at the national level.

Why do CSAs Cause Such Great Concern?

There are several reasons why CSAs pose risks previously unknown with more traditional drugs of abuse. At least three medical hazards have already come to light and, as these substances become more prevalent and the demand grows, as seems destined to happen, more may become apparent. In this section, we will discuss the reasons why these compounds pose such a serious public health hazard.

First, these newly designed and highly tailored look-alikes are unknowns, having been produced and sold with little regard to their biological effects. This is in dramatic contrast to the legitimate development of a new drug. For example, when a pharmaceutical company develops a new drug, years of testing in laboratory animals are required to assess potential toxic effects before any compound is made and given to humans. However, when a new compound is made and marketed by an illicit chemist, the addicts

themselves are the first to try it. In this sense they truly are human guinea pigs. If the compound has the desired effects, and is not a poison, an illicit drug dealer may have a "winner" in terms of sales and profits while at the same time being "beyond the reach of the law." If, on the other hand, a new toxin has been produced, the addicts themselves are the first to know, and it's impossible to predict how long it will take before the damage is discovered. It is our impression that even this may not matter until sales have been seriously affected.

Secondly, there are very few, if any, quality controls in these underground laboratories, some of which are located in garages or basements. Even the most meticulous chemist cannot always carry out reaction schemes perfectly, so the risk of producing undesired by-products remains ever present. Pharmaceutical companies, therefore, constantly monitor the purity of any given product (in other words, they have quality controls built in). Illicit laboratories seldom have the facilities to do this. It is highly unlikely, therefore, that such procedures are carried out, at least not after the original synthesis has been successfully executed. This type of error led to the synthesis of MPTP and its devastating consequences, something which we will return to later.

Thirdly, some of these synthetic analogs are structurally redesigned narcotics which are more potent than the drugs they resemble. Some of the fentanyl analogs (of which there are now seven "popular" variations) are between 2000 to 7000 times more powerful than morphine. This potency makes the dosage difficult to titrate, increasing the likelihood of overdose. There have been over 100 overdose deaths in California alone. Additionally, this potency makes fentanyl and its analogs significantly more addictive than existing street drugs because of its rapid rush and remarkable high.

Given the foregoing, one would have predicted that a toxic substance with harmful qualities was bound to emerge from one of these underground laboratories. As we will see, this is precisely what happened in northern California in the summer of 1982.

The First "Designer Drug Disaster"

Our first introduction to this new phenomenon occurred in northern California in the Summer of 1982, when we began seeing young heroin addicts with a clinical condition virtually identical to Parkinson's disease, a disease which typically occurs in the elderly (Langston et al, 1983). It was soon discovered that the offending agent was MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Apparently an illicit chemist had been attempting to produce an uncontrolled analog of meperidine (Demerol) known as MPPP (1-methyl-4-phenyl-4-propionoxypiperidine), using a formula originally described in 1947 (Ziering et al, 1947). This chemist was working in a garage in Morgan Hill, California, which became quite hot in the summer months. When using the Ziering formula, either too much heat or acid leads to the production of a by-product, MPTP. Although MPTP was not generally known to be toxic at that time, it is interesting to note that the company that Ziering himself had worked for in the 1940's had found that MPTP was toxic in animals, but the results were never published. While it's clear that MPPP was successfully produced and sold as synthetic heroin in northern California for a brief period, the inevitable eventually happened (probably on a hot summer day) and a batch of pure MPTP was made and sold. Tragically, the addicts who bought and used this

substance have suffered permanent damage to their nervous systems (MPTP is now known to be one of the most selective neurotoxins ever discovered). Seven of these individuals now require medication every two to three hours just to be able to move. Working in conjunction with the Centers for Disease Control (CDC), we have now identified over 500 addicts who may have been exposed to MPTP, and there is reason to believe that all of them may be at risk for developing parkinsonism at some time in the future.

Other Medical Consequences

The MPTP tragedy represents an error in quality control. Fentanyl analogs have proven hazardous (at least to the inexperienced user) because of their extraordinary potency. To date we have not yet seen a documented example of the third type of error; that is, the production of a new compound which has proven to actually be toxic. However, there is now increasing concern that this may have finally happened as well.

In the summer of 1986, the Western Laboratory of the Drug Enforcement Administration in San Francisco, California sponsored a conference bringing together members of the medical, scientific, law enforcement and regulatory community to discuss increasing reports of a choreiform disorder remarkably similar to a neurological condition known as Huntington's Chorea, after use of a street drug. We actually encountered our first case of this disorder in 1984. A 32 year-old carpenter had injected a substance he thought was heroin and within an hour had developed continuous jerking movements of his trunk and limbs. They have continued to this day, and have proved to be disabling. In the last six months, over 20 cases of acute chorea have been identified in two northern California counties, and all of the evidence points to a new, toxic methamphetamine analog. We may or may not learn the exact identity of the offending agent, but our fear is that it represents another in a series of new and toxic products to emerge from the laboratories of our nation's illicit chemists.

These are probably just a few of the problems which have occurred as the result of CSA abuse. It seems likely that CSAs have caused many problems which have never come to light, whether through ignorance or fear. Most addicts will not report adverse effects of drugs (sometimes even if their lives are threatened- for example, one of our first MPTP patients was unwilling to seek help after exposure, in spite of the fact that she was immobile and completely frozen. Her family had to feed, dress and bathe her daily for weeks until she was finally located and urged to seek medical assistance). Hence, what we have encountered so far may be just the tip of the iceberg.

The Future

In the previous sections of this article, we have outlined the nightmarish problems CSAs present for those willing to take street drugs of any form. These individuals literally are playing a form of Russian roulette, only the bullets aimed at their brains are chemical ones rather than being made of lead. As bad as all of this is for addicts, the advantages for those producing and selling these compounds are almost unbelievable. First, there is no need for overseas connections, eliminating all of the problems related to importing a product, including the need to smuggle their wares in, often at great personal risk. Secondly, as we have already pointed out, CSAs are not controlled, thereby eliminating another major risk. However, these advantages pale when we come to the

issue of profits, which are potentially astronomical. Five hundred dollars of precursor chemicals can be turned into a product which has a street value of several million dollars. It's unclear to us whether or not this last incentive can ever be overcome.

Given all of these advantages, why haven't CSAs exploded on the drug scene, and spread like wild fire throughout the country? Two years ago, we predicted that they would. The reason they did not now seems apparent. "Organic" heroin and cocaine have remained so plentiful and inexpensive that there has been little incentive to shift to these new synthetics. The illicit drug industry probably has just as much intertia as legitimate industry and might be expected to respond to the same market pressures. Now the situation may be changing. A major campaign is about to be launched by the current Administration, not only to fortify the borders of the United States against drug traffic, but also to assist countries where these narcotics originate to stop their production and export to the United States.

If successful, this well-intended initiative seems destined to provoke a shift to the production of synthetic drugs. Furthermore, once dealers are compelled by enforcement measures to turn to CSA production and realize the attractive features outlined above, there may be no turning back. Given the hazards we have outlined above, our previous drug problems may look mild by comparison. There have been indications that manufacturers have already begun to adapt - underground laboratories are producing amphetamine and methamphetamine alternatives for cocaine users and PCP is being added to parsley as a marijuana substitute. What will be the additional health hazards of this new push towards CSAs? The implications could be enormous. For example, the estimated cost of caring for one severely affected MPTP patient for one year is $20,000. Let us assume that the next CSA has toxic effects which damage the kidney and that 1000 addicts were affected by this new toxin. The cost of dialysis per year is approximately $34,000 per patient; hence, over $30,000,000 per year would be required to care for these patients, not to mention the cost in terms of human suffering.

Dealing with the CSA Problem: A Comprehensive Approach

Our point here is not to offer a definitive solution to the problem. If one thing has become clear from the many hearings and meetings on CSAs, it is that there is no immediately obvious solution. What then can be done? We believe that a comprehensive program is needed to assess the current situation so that the beginnings of a rational approach to the looming dangers of CSAs can be formulated. At the moment, no such comprehensive approach exists. Those who are currently struggling with the problem (our research group included) are each approaching it from their area of expertise and perspective. If progress is to be made, we believe that a comprehensive overview of the current situation must be obtained. Mechanisms for information processing (input and output, see below), education (for both users and health care professionals, as well as for law enforcement personnel who may come in contact with the drugs themselves), drug sample analysis, epidemiologic activities, on-line medical consultation, and the assistance and involvement of legislative, law enforcement and health professionals must be available and properly coordinated. We have proposed such a comprehensive approach to the State of California. This program could easily be modified for implementation at the national level.

A. The Information Component

As noted above, the first step in dealing with CSAs is to obtain and maintain a clear assessment of the current situation. To do this, an information network must be established which not only has the capability to collect data but can disseminate that data in a meaningful form on a timely basis (i.e., through monthly or quarterly updates, with a provision for emergency bulletins as warranted). Data on availability of CSAs could be collected in a number of ways. We have, in our work for the State of California, utilized an Anonymous Samples Program, whereby addicts can submit a sample of a potentially bad drug and receive a response within one to two weeks. Other potential sources of samples would be government and law enforcement agencies, as well as hospital emergency rooms, private toxicology laboratories and drug treatment programs. There are currently several programs available to do just this (i.e., the Domestic Monitoring Program [DMP] supported by the Drug Enforcement Administration); however, in order for them to be effective, data from all of these sources need to be collected, collated and interpreted in a meaningful way.

Additionally, epidemiological studies (such as our outreach program, implemented to locate and follow the individuals exposed to potentially toxic CSAs) should provide another source of data for the informational network. These epidemiological efforts (whereby the addict population is directly monitored for new syndromes, toxic reactions and specific drug-use prevalence), when combined with the ability to analyze samples in a coordinated manner, represent a way to quickly pin-point problems as they arise.

If all of the foregoing information is analyzed and collated, it could form a basis for developing the first coherent picture of the current status of CSAs in this country. This information could then be made available in a variety of ways, including publications, telephone "hotlines" (through which both addicts and agencies could contribute and receive updates), and perhaps even a computer bulletin board which would allow for 24-hour access.

B. The Education Component

The short-term success of a potential solution to the CSA problem depends to a large extent on acquiring and maintaining an accurate overview of the current situation. The long-term success of the program lies in educational efforts designed to warn potential users and enable health professionals to better deal with the problems they are facing.

The first and most obvious element of such an educational program should be a speakers program, provided by individuals able to address the problems raised by CSAs for a number of different audiences. Groups which could be aided by such a speakers program include treatment personnel (to answer questions relating to problems that they are seeing in their clients), federal, state and local agencies (for informational updates on the current situation), and law enforcement groups (for information on the occupational hazards of exposure to these possibly toxic substances and their place of manufacture). Education could also be important and useful in a preventative manner. A speakers program illustrating the hazards and consequences of CSA abuse (using the MPTP story as an example) could play a role in altering the behavior of those not yet committed to a life of drug abuse.

However, to institute such a program at the national level, it may be

necessary to use video tape presentations, pamphlets, and similar educational materials to introduce interested parties to the problem, giving direction as to where to obtain further information and help.

C. Analytic Investigative Laboratories

Paramount to maintaining an accurate overview of information regarding CSA availability is the capability to analyze and identify samples from all available sources. Without the capabilities to analyze biological and solid samples and to identify new compounds as they become available, the information and educational components of a comprehensive program will fail due to lack of current knowledge. For a national program, we would suggest the establishment of regional laboratories, uniformly equipped and linked as part of the information network. These laboratories need to be capable not only of testing for known substances of abuse but of providing standard reference materials for state/local laboratories to enable them to assist in the identification of these compounds. Most importantly, they must be able to identify new compounds as they appear on the streets. It is important to note that this component should work closely with the epidemiological and medical aspects of the program so that correlations between new toxic reactions and the appearance of new CSAs can be made quickly. The DEA already has such a network of laboratories in place, but they primarily analyze samples collected by their own agencies. Ideally, a designated number of these laboratories should be able to test for biological toxicity in these substances. Such testing could greatly accelerate efforts to schedule and control new and dangerous compounds. Without the capability of performing toxicological studies, both addicts and federal and local authorities involved will remain blinded to the risk of the substances. It may be necessary (and advisable), due to the cost of maintaining facilities for such testing (i.e., the purchase of test animals, their board and care, etc.), to have only selected regional laboratories test for CSA toxicity and distribute their findings through the informational component of this program.

D. Epidemiologic Input

Identifying the demographic distribution of various types of substance abuse is another important part of maintaining an accurate assessment of the problem posed by CSAs. Further, ongoing monitoring of the drug abuse community for patterns of substance abuse can be very helpful in discovering new compounds and predicting new trends of this abuse. Finally, in-depth study of the first designer drug disaster could prove helpful in dealing with new problems as they arise.

E. Medical Component

As outlined earlier, the potential health hazards of CSAs constitute one of the major reasons that these new compounds are of such concern. We propose that a medical component be included in the comprehensive approach to this problem for several reasons.

First, the medical component should identify and delineate the effects of new CSAs in humans. Information regarding the medical, neurological and psychological effects of a newly identified, potentially toxic CSA needs to be collected and recorded, evaluated, and, when appropriate, disseminated. Without this step, appropriate treatment programs, a second imperative of this component, cannot be formulated.

Thirdly, representatives of the

medical component must be available to health professionals for consultation on an on-going basis. Continuous monitoring of long-term care and treatment programs will help maintain the initial comprehensive overview of the CSA problem.

Additionally, the medical component should join epidemiological and anayltical efforts to assess the possible health hazards of any new epidemics as they develop (see below).

Finally, long-term medical follow-up of CSA-related problems is essential. Our studies with MPTP have shown that limiting medical evaluations to a single point in time may lead to an erroneous assessment of the problem. For example, 90% of the MPTP-exposed cohort are asymptomatic at this time, yet tests done on a number of these individuals with advanced positron scanning techniques show subclinical damage to the nervous system, and therefore they may be at risk for a parkinsonian condition in the future. Had follow-up studies not been done, this "pre-clinical" condition would have escaped our attention altogether.

F. Coordination of Efforts in Emergency Situations

We also recommend the development of a response team, available to be "on-site" should the appearance of a new and toxic CSA be suspected. In a situation such as the recent cases of patients experiencing choreiform movements possibly due to exposure to a synthetic methamphetamine in the northern San Francisco Bay area, or the recent outbreak of unexplained deaths in California's Santa Cruz County (attributed at this time to an unknown "synthetic heroin"), the proper response, that of sending in such a qualified team, was needed; but, no mechanism was in place to provide such a team. This response team, made up at the very least of a physician, a toxicologist and an epidemiologist experienced in these problems, may have the only opportunity to discover the cause of such outbreaks. Such immediate investigation and intervention represent the best hope of avoiding future designer drug disasters, at least on a large scale. At the national level, the Centers for Disease Control (CDC) might take a lead role in providing these resources.

In addition to this team, the availability of a central medical hotline for consultation purposes (to hospital emergency rooms, law enforcement agencies, treatment personnel, government agencies, etc.) would be invaluable to people dealing with these problems on the front lines, most of whom are under pressure to sort out these medical emergencies.

Conclusions

In this article, we have attempted to summarize both the hazards of CSAs and why we may expect to see many of them in the near future. We have also proposed a general outline of what can be considered a comprehensive approach to the problem. However, most of the components of this program are passive or reactive. In other words, they are primarily designed for information gathering or to respond to situations as they develop in the community (i.e., the appearance of new CSAs or perhaps a toxic designer drug outbreak). In our opinion, this is the most that can be done at this time other than to utilize increasingly tough measures on the law enforcement side. However, there is an important long-term goal which underlies the conceptual nature of this comprehensive program which we are suggesting. As additional information is gained and a clearer picture of the nature of the problem is defined, more active or interventional programs can be

rationally developed. Once all the features of this program are in place, potential solutions may declare themselves. This program could be of invaluable assistance to legislative bodies attempting to develop ways to cope with what may be a major public health problem, not to mention the social aspect of the drug abuse problem. Hence, what we have suggested is put forth only as a first step. However, as in any scientific endeavor, once a better understanding of the problem has been achieved, a more rational and, hopefully, effective attack on the problem can be instituted.

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SAFETY IN HANDLING THE FENTANYL ANALOGS

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Introduction

The fentanyl family of narcotic analgesic agents are potent analogs of morphine which have been made available to and widely accepted by the medical community for a variety of surgical procedures since the late 1960's.

In the late 1970's, the Drug Enforcement Administration became aware that analogs of fentanyl were synthesized illicitly for the purpose of street sale. In the state of California, various analogs of fentanyl were found as ingredients in "synthetic" heroin and in serum and urine samples of users and overdose victims.

Abuse of fentanyl and its analogs is not limited to the criminal element but includes the health professionals as well. Increasing awareness of abuse by nurses and physicians has resulted in internal efforts by the medical profession to stop the abuse. In the horse (and dog) racing industry, abuse of many drugs, including the fentanyl analogs, has been a chronic problem as narcotics may, in small doses produce a stimulatory effect in these animals.

Over the last few years various state drug abuse agencies and the Drug Enforcement Administration have appealed to Janssen to assist in an effort to overcome this problem by providing technical information on the fentanyl narcotics, assay techniques and residue analysis services.

The safety and handling techniques described will be restricted to our commercialized fentanyl analogs. Toxicological, physical-chemical and potency data are presented to familiarize the reader with their nature. Our experience is minimal with illicit fentanyl analogs as only a few have been tested in the Janssen screen for ethical drugs.

History

Janssen Pharmaceutica is an ethical pharmaceutical firm, located in Beerse, Belgium which is in the northern portion of the country near the Dutch border. For more than 25 years, Dr. Paul Janssen and his researchers have conducted extensive research in the field of narcotic analgesics which has led to a series of these compounds described as the fentanyl analogs (N-substituted phenylpiperidines).

Our interest in anesthetic analgesics started in 1953 and was stimulated by the discovery of dextromoramide in 1956. This was followed by the synthesis of a derivative of meperidine called phenoperidine (Fig. 1). The first four aminopiperidine derivatives developed were found to be about three times more potent than morphine. In 1960, fentanyl became the first 4-anilinopiperidine derivative to be produced and a major step in the development of potent narcotic

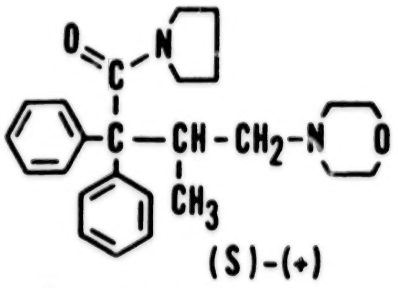
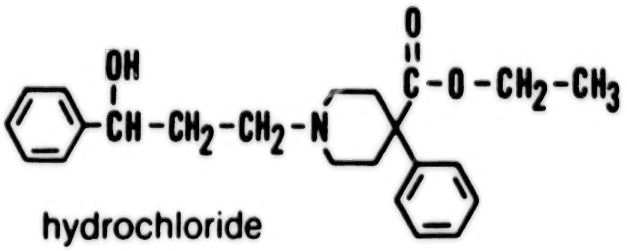
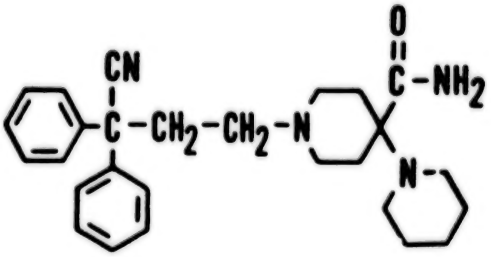
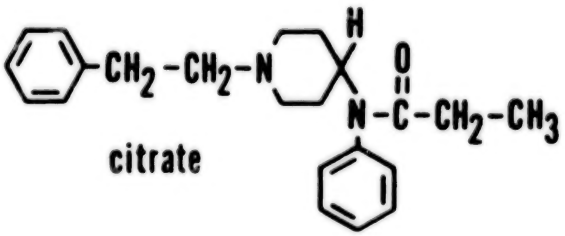
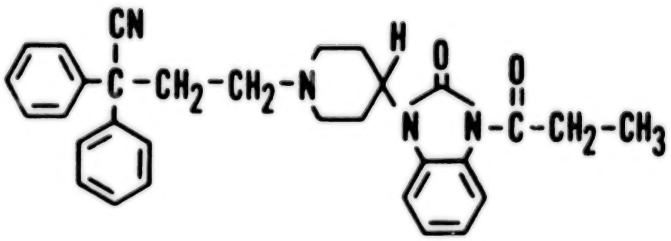
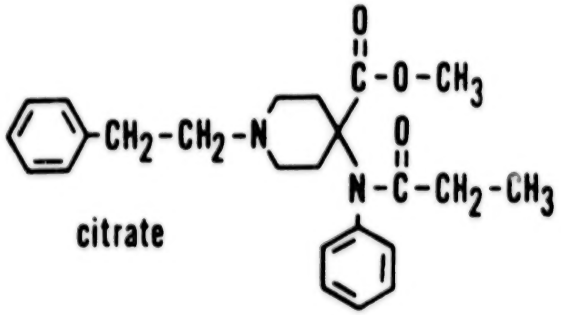
Dextromoramide	R 875	1956	 (S)-(+) D-tartrate
Phenoperidine	R 1406	1957	 hydrochloride
Piritramide	R 3365	1960	
Fentanyl	R 4263	1960	 citrate
Bezitramide	R 4845	1961	

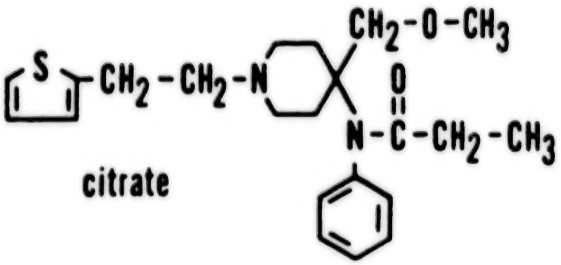
Figure 1

Carfentanil R 33799 1974



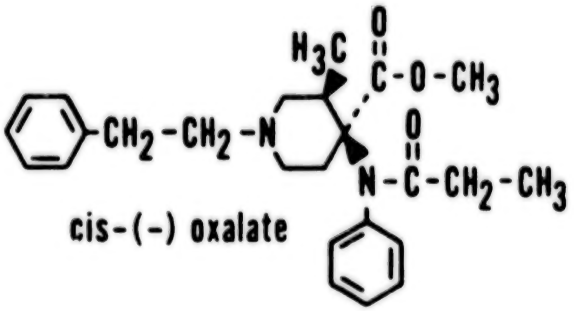
citrate

Sufentanil R 33800 1974



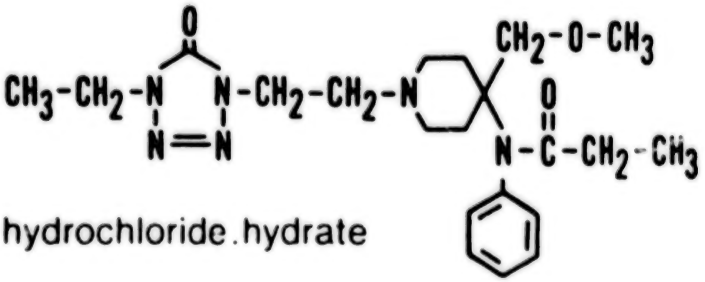
citrate

Lofentanil R 34995 1975



cis-(-) oxalate

Alfentanil R 39209 1976



hydrochloride.hydrate

Figure 2

analgesics. Fentanyl (marketed as SUBLIMAZE™) was well over 500 times more potent than meperidine and had a higher safety margin. The main thrust behind the Janssen research for fentanyl derivatives was to provide safer and more potent narcotic analgesics.

The resulting family of narcotic analgesics has been commercially developed here and abroad (Fig. 2). The next one, carfentanil is the most potent narcotic analgesic developed to date and was patented in 1974. Due to its potency, the compound has been used in animals, specifically for controlling herds of large wild animals such as elephants and rhinoceros. It is currently being developed in the United States by a company, Wildlife Laboratories, Inc., in Fort Collins, Colorado.

Sufentanil is currently marketed by Janssen Pharmaceutica as SUFENTA™ in the United States. It is another very potent analog of fentanyl, which has a long duration of analgesic action but with minimal cardiovascular effects. Hence, it is a very safe anesthetic analgesic for use in long surgical procedures. Lofentanil, on the other hand, only slightly different in structure, is very potent but with a narrow safety margin. The decision was made not to develop this compound because of the extreme hazard in its use. In our experience, it is extremely difficult to reverse the narcotic effects of this compound with the use of standard reversal agents, such as naloxone. Finally, alfentanil is a very short acting narcotic analgesic which is intended for minimal procedures in surgery. This compound is approximately as safe as fentanyl, slightly less potent and very short acting. When marketed, it will likely be used extensively in short procedures such as those performed in the dentist's office or in out-patient clinics.

Potency

In Table 1, fentanyl analogs commercialized by Janssen are arranged in order of increasing potency and compared with meperidine (pethidine). The safety margin, which is a ratio of the effective dose to the lethal dose, for meperidine is quite low, while those for alfentanil and fentanyl are much higher. Sufentanil was chosen to be developed for long term surgical procedures because of its safety margin. The safety margin for lofentanil is extremely low while that for carfentanil fairly high. There were only slight structural modifications required to make these significant changes in safety and in potency.

Modification in the C-4 position of the piperidine ring may cause increases in potency while modification at the C-3 position usually results in increased duration of action and potency (Van Bever, 1974). In general, modifications resulting in greater potency usually mean less toxicity while any modification which lengthens the duration of action in these compounds will usually increase their toxicity (Van Bever, 1986). For example, the analgesic effect of lofentanil can last up to 48 hours and thus it is the longest acting fentanyl compound produced to date.

Chemistry

Table 2 shows that the physico-chemical characteristics of the five commercial analogs are quite similar. All compounds are in the citrate salt form, except for alfentanil, a hydrochloride and lofentanil, an oxalate salt. Melting points range between 130 and 180°C. There is no known measurable vapor pressure of these salts and solubility is high in water and low molecular weight alcohols.

Table 1

The Potency Ratio and Safety Margins of Fentanyl Analogs Compared with Pethidine (Meperidine)

Compound	*Lowest ED_{50} mg/kg*	*LD_{50} mg/kg*	*Safety margin*	*Potency ratio*
PETHIDINE	6.0	29.0	4.8	1
ALFENTANIL	0.044	47.5	1080	137
FENTANYL	0.011	3.1	277	550
SUFENTANIL	0.00071	17.9	25211	8500
LOFENTANIL	0.00059	0.066	112	10200
CARFENTANIL	0.00034	3.4	10000	17800

Table 2

Physico-Chemical Characteristics of Fentanyl Analogs

	Fentanyl	*Alfentanil*	*Sufentanil*	*Lofentanil*	*Carfentanil*
Mol wt.	529	453	579	499	587
Melt. Pt. (^{o}C)	149	138	136	178	153
Water Sol. (g/l)	25	142	46	23	18.5
Fat Sol. (mg)	2	5	unknown	unknown	unknown
Octanol/H_2O Coefficient	4.05	2.16	3.95	4.22	3.85
MeOH Sol. (g/100 ml)	10	50	28	60	40
Ethanol Sol. (g/100 ml)	0.76	20	2.1	9.2	3.4
$CHCl_3$ Sol. (g/100 ml)	0.3	50	1.2	60	11

Table 3

Acute Toxicology of Fentanyl Analogs as Measured by LD_{50} (mg/kg)

Compound	Route of Administration		
	I.V. Mouse	I.V. Rat	I.V. Dog
FENTANYL	10	3.5	7.5
ALFENTANIL	73	47	73.5
SUFENTANIL	18.7	17.9	14.1
CARFENTANIL		3.4	4.8
LOFENTANIL		0.066	0.66

Toxicology

The commercial analogs are compared in terms of toxicological properties in Table 3. There is a wide range of toxicological potency in these compounds considering their similar structures. Hence, in the illicit production of fentanyl analogs it is conceivable that someone could produce a compound that is extremely toxic which could not be predicted on the basis of its structure. For example, i.v. toxicity in rats can vary as much as 1,000 fold between lofentanil and alfentanil while the variation in the dog is 100 fold. Consequently, human toxicity characteristics of fentanyl analogs are not predictable.

Illicit Analogs

Potency data for four of the illicit analogs identified by the DEA are compared with those data from the commercialized analogs that Janssen has produced in Table 4. The thienylfentanyl analog has been seen "in the street." The alpha-methylfentanyl was the first identified "China White" and 3-methylfentanyl has recently been sold as "China White." The p-fluorofentanyl analog has also been found in "street" samples. Fortunately these illicit analogs have potencies similar to fentanyl (except 3-methylfentanyl) which may allow relatively easy detection in body fluids. Extremely potent analogs found in nanogram blood levels may be difficult and challenging to detect and confirm.

Safety

The safe handling of the fentanyl analogs begins with protective clothing always worn by production people in manufacturing units in Belgium and the USA where fentanyl is put into vials. When handling the raw drug, they employ a compressed air mask or work in a hood. In Belgium, the unit operators wear an air stream helmet, Type AH-1 - Racal, which gives not only head, but eye and face protection. The fine filter is designed to meet filtration efficiency requirements of a BS 2091 type A dust filter (Haagen, 1986). It removes up to 90% of all airborne particles above 5 micrometers in diameter. Filtered air is directed over the user's forehead and exhausted at the bottom of the visor

Table 4

Potency Comparisons - Commercial/Illicit Fentanyl Analogs
as Measured by the ED_{50} (mg/kg) in the Tail-Withdrawal Test in Rats

Compound	*Route of Administration*		
	Oral	*I.V.*	*S.C.*
Fentanyl	0.11	0.01	0.014
Alfentanil		0.04	
Sufentanil		0.0008	
Carfentanil		0.0005	0.0007
Lofentanil		0.0005	0.06
Thienylfentanyl	0.31	0.015	0.035
Alpha-methylfentanyl	0.05		0.015
3-methylfentanyl (trans)		0.01	
Para-fluorofentanyl	0.02		

Table 5

Overdose Symptoms for Commercially Available Fentanyl Analogs

Nausea	Weakness
Obstipation	Palpitations
Fatigue	Slow Pulse
Irritability	Difficulty Breathing
Sedation	Impaired Circulation
Restlessness	Hypotension
Vertigo	Coma

adjacent to the chin. It is not an "operator-friendly" unit but is more protective than a compressed air mask. The operators involved in the production wear gloves and disposable clothing during the weighing of the raw compound. There is always a second person present when these compounds are being handled in large quantities to provide first aid if necessary.

Overdose symptoms extrapolated from patient data obtained when treated with fentanyl reflect the potency of these compounds (Janssen Pharm., 1981). These symptoms are listed in Table 5. Even though these data relate to fentanyl they may be used as a guide to recognizing symptoms that may be seen in those overcome by fentanyl analogs. In brief, any officer working in a clandestine lab and exhibiting these symptoms should be treated with appropriate first aid procedures immediately. Material safety data sheets containing these data for the commercialized fentanyl analogs are available upon request from Janssen Life Sciences Products.

The first aid treatment for someone overexposed to fentanyl analogs is expressed as a function of the type of exposure. For accidental oral intake, wash out the mouth of the victim as much as possible and keep the victim awake while notifying a physician. Gastric lavage is indicated with aqueous permanganate or some other appropriate purgative (Janssen Pharm., 1985). When fentanyl analogs come in contact with skin, it is important to wash thoroughly with soap and water. No information exists regarding fentanyl transmission through dermal layers but a fentanyl "patch" currently under development is to be used specifically for pain relief. When fentanyl contacts the eye one should rinse thoroughly with running water, keeping the lids open.

Inhalation is by far the most severe hazard in handling large quantities of these compounds. It is important to remove the victim to fresh air and apply artificial respiration and/or a source of oxygen. The patient should be kept awake until a physician arrives. The commercial fentanyl compounds do not have extensive vapor pressure in the salt form but toxic aerosols could be formed from aqueous solutions.

The most important agent to be carried by anyone handling suspected fentanyl analog compounds is an antidote, the narcotic antagonist, naloxone. Naloxone is the reversal agent of choice due to its relative safety. One fentanyl analog, lofentanil, however, is so potent that it's associated narcosis is difficult to reverse. As the effects of naloxone wear off before the effects of a long acting narcotic analgesic (i.e., carfentanil) it may be necessary to repeat dosage (Table 6).

Clearance of Spills

The following steps should be taken for the clearance of any spilled product. In handling spills of bulk fentanyl (large quantities) the person cleaning should always wear a compressed air mask, disposable clothes and gloves. The area around the spill should be marked for easy identification and cleaning after the material is removed. The swept material should be sealed in metal containers. It is important to wash affected areas of the skin with excess soap and water (Janssen Pharm., 1985).

Conclusion

The motivation behind the development of potent fentanyl compounds was the associated increase in their safety ratio for surgical use. Unfortunately that same search has benefited

Table 6

Important Reversal Agent Treatment for Fentanyl Overexposure

MEDICATION
Naloxone - 1 cc admin. s.c., i.m. or i.v. - if necessary repeat every 2-3 minutes
Nalorphine - 5-10 mg i.v. - if necessary repeat every 10-15 min - max 40 mg

individuals who have a different application in mind. Janssen Pharmaceutica and, specifically the Janssen Life Sciences Products Division will help law enforcement officials, medical professionals, toxicology labs or anyone involved in the monitoring and analysis of these compounds in their efforts to eliminate the improper use of fentanyl and its analogs.

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BRAIN CELL DESTRUCTION CAUSED BY AMPHETAMINES AND RELATED COMPOUNDS

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Methamphetamine (MA) is one of the prototypic psychomotor stimulants. In the past, it has been widely used to suppress food intake and increase mental alertness and physical endurance. Methamphetamine and related stimulant phenethylamines can also induce an elevation in mood. This has led to the use of the drug for nonmedicinal purposes. Amphetamine (AMPH) and related compounds have also been used to treat obesity, depression, narcolepsy, attentional deficit disorder in children, and residual symptoms of attentional deficit disorder in adults. Tolerance develops to the anorectic effects of AMPH and the dose is often increased; therefore, the permanent (i.e., toxic) effects of AMPH and related compounds are of concern. Among the undesirable effects of AMPH that occur with large doses is amphetamine-induced psychosis. The amphetamine psychosis includes symptoms of paranoid delusions, disordered thought, inappropriate aggressive behavior, and hallucinations. When a drug history is not available, it is difficult to discriminate an amphetamine-induced psychosis from an acute psychotic episode prognostic of schizophrenia (see Costa and Garattini, 1970; Seiden and Dykstra, 1977; Goodman and Gilman, 1980; Ellinwood and Kirby, 1977). More recently methylenedioxyamphetamine (MDA) and methylenedioxymethamphetamine (MDMA) have been used for their hallucinogenic activity or their alleged psychotherapeutic effects respectively (Greer and Strassman, 1985).

Since the psychomotor stimulants as a class have a range of effects, their neuropharmacology, behavioral pharmacology and possible neurotoxicity have been focal points for studying interrelationships among transmitter chemistry, drugs, and behaviors (Carlsson, 1970; Chiueh and Moore, 1975; Creese and Iversen, 1973, 1975). During the early 1970's substantial evidence accumulated which suggested that the effects of amphetamines and related drugs were mediated by the dopamine (DA), norepinephrine (NE), and 5-hydroxytryptamine (5HT) transmitter systems in the brain (Moore et al, 1970; Green and Harvey, 1974; Mabry and Campbell, 1973; Creese and Iversen, 1975). This evidence suggested a subsequent question of whether changes in the DA, NE or 5HT systems occur as a result of prolonged administration of AMPH.

Changes in these transmitter systems were assessed in rhesus monkeys 3 to 6 months after the end of chronic MA administration. The monkeys were given high doses of MA (3.5 to 6.0 mg/kg every 3 hours, with the total daily dose between 28 and 48 mg/kg per day) administered intravenously. In spite of the high dose, the monkeys in these studies became tolerant to the disruptive effects of MA as measured by operant task and feeding (Fischman and Schuster, 1977). There

Table 1. Effects of Methamphetamine on Monkeys

A. Brain Levels of NE (ug/g tissue) Following Several Months of 8 Daily Injections of Methamphetamine (Meth.)

Treatment	*Pons-medulla*	*Midbrain*	*Hypothalamus*	*Frontal cortex*
Control N = 12	0.45 ±0.04	0.59 ±0.03	1.80 ±0.26	0.21 ±0.03
24 h post chronic meth. N = 5	0.23 ±0.07*	0.40 ±0.06*	0.76 ±0.18*	0.08 ±0.23*
3-6 months post chronic meth. N = 6	0.31 ±0.08	0.39 ±0.07*	1.40 ±0.43	0.10 ±0.01*

* = $p<0.05$ vs control

B. Brain Levels of NE (ug/g tissue) Following Two Weeks of 8 Daily Injections of Methamphetamine (Meth.)

Treatment	*Pons-medulla*	*Midbrain*	*Hypothalamus*	*Frontal cortex*
24 h post chronic meth. N = 3	0.21 ±0.11 (48%)	0.41 ±0.12 (69%)	1.77 ±0.23 (98%)	0.12 ±0.04 (57%)
2 wk post chronic meth. N = 3	0.40 ±0.01 (88%)	0.48 ±0.02 (81%)	1.4 ±0.34 (77%)	0.11 ±0.01 (52%)

(Numbers in parentheses show % of control)

Selden, L.S., Fischman, M.A., and Schuster, C.R., *Drug and Alcohol Depend. 1*, 215-219, 1975/1976.

Table 2. Effects of Methamphetamine on Monkeys

A. Brain Levels of DA (ug/g tissue) Following Several Months of 8 Daily Injections of Methamphetamine (Meth.)

Treatment	*Pons-medulla*	*Midbrain*	*Hypo-thalamus*	*Caudate*	*Frontal cortex*
Control N = 12	0.16 ±0.01	0.51 ±0.04	0.83 ±0.12	10.10 ±0.57	0.09 ±0.01
24 h post chronic meth. N = 5	0.51 ±0.20 ns	0.61 ±0.11 ns	1.33 ±0.30 ns	**2.00 ±1.00 p<0.001**	0.19 ±0.04 ns
3-6 months post chronic meth. N = 6	0.13 ±0.03 ns	0.33 ±0.07 ns	0.82 ±0.17 ns	**3.15 ±0.64 p<0.001**	0.13 ±0.05 ns

B. Brain Levels of Dopamine (ug/g tissue) Following Two Weeks of 8 Daily Injections of Methamphetamine (Meth.)

Treatment	*Pons-medulla*	*Midbrain*	*Hypo-thalamus*	*Caudate*	*Frontal cortex*
24 h post chronic meth. N = 3	0.19 ±0.01	0.43 ±0.07	1.14 ±0.53	3.67 ±0.50	0.15 ±0.02
2 wk post chronic meth. N = 3	0.53 ±0.98	0.76 ±0.14	1.20 ±0.45	2.30 ±0.37	0.30 ±0.01

Selden, L.S., Fischman, M.A., and Schuster, C.R., *Drug and Alcohol Depend. 1*, 215-219, 1975/76.

was a loss of DA in the caudate nucleus but not in the hypothalamus, and also a small change in the level of NE in the brainstem. The results with 5HT were not clear. The DA depletion 3 to 6 months after the last MA injection suggests that the changes in DA were permanent (Tables 1 and 2).

Since the monkeys tested in the early studies were administered MA for a period of 3 to 6 months, we wondered how critical the long period of high dosing was to create the apparently irreversible damage to the DA system. Therefore, three rhesus monkeys were treated on a 2-week regimen of MA injections. These monkeys were injected with a total dose of 16 or 24 mg/kg per day divided into eight intravenous (i.v.) injections. The control monkeys for these studies were eight rhesus monkeys from the Wisconsin Primate Center; these monkeys had not been given any psychotropic drugs. After 2 weeks of MA injections, the monkeys were MA-free for 2 weeks and then they were sacrificed and the brains analyzed for catecholamines. As with the monkeys that were injected for longer periods of time, the monkeys injected with MA for 2 weeks showed depletion of DA. We speculated that this depletion may be indicative of permanent damage to the DA system.

There is strong evidence that AMPH and related drugs block reuptake of DA, NE and 5HT, inhibit monoamine oxidase, and cause release of DA from the cytoplasmically bound pool (Seiden and Dykstra, 1977; Cooper et al., 1974). Release and blockade of reuptake would tend to deplete levels of DA in the nerve endings in the presence of MA. However, MA-induced depletion would not be expected to last for more than several hours in the absence of MA (Ricaurte et al., 1980). Therefore, on empirical and theoretical grounds, the DA depletion seen in the monkeys weeks or months following the cessation of MA administration is not caused by the acute effects of MA.

The early research using monkeys raised several questions: 1) was the DA depletion seen in the rhesus monkey specific to monkeys, or would rats, mice, guinea pigs and other animals show the same response to MA; 2) was the depletion specific to MA, or would other psychomotor stimulants (e.g. AMPH, methylphenidate) that were structurally or functionally related to MA cause a similar depletion of DA; 3) were other transmitter systems besides DA and possibly NE depleted by exposure to MA; 4) what were the minimal times and doses that would produce significant DA depletion; and 5) were nerves destroyed or was the synthetic and/or storage capacity of the dopaminergic cell compromised? The data necessary to answer these five questions also helped to elucidate the chemical mechanism by which MA and related drugs caused the long-lasting depletion of DA and other transmitters.

Prolonged doses of MA caused depletions of DA in the rat and the guinea pig as long as 8 weeks after the last administration of MA. Furthermore, the depletions seen 2 weeks after discontinuing MA were not different from the depletions seen 8 weeks after discontinuing MA (Wagner et al., 1980b; Ricaurte et al., 1980). These results, summarized in Tables 3 and 4, indicate that MA toxicity is a general phenomenon occurring in the rhesus monkey, mice, rats, guinea pigs and cats (Steranka and Sanders-Bush, 1980; Levine et al., 1980). Since the MA-induced toxic response (DA depletion) occurs in several species of animals, it may also be an important side effect of chronic administration of high doses of psychomotor stimulants in humans.

The duration of the depletion suggested that nerve cells or nerve

Table 3

Effects of Methamphetamine on Regional Brain Catecholamine Levels in Rats

Treatment	*N*	*Caudate*	*Telen-cephalon*	*Midbrain*	*Pons-medulla*
		DA	*NE*	*NE*	*NE*
Vehicle	10	8.67 ±0.67	0.34 ±0.02	0.69 ±0.04	0.50 ±0.03
25 mg/kg per day d-meth.HCl	3	6.44 ±0.88	0.29 ±0.04	0.71 ±0.05	0.45 ±0.05
50 mg/kg per day d-meth.HCl	11	3.47 ±0.41	0.35 ±0.03	0.66 ±0.07	0.50 ±0.03

Rats received subcutaneous methamphetamine hydrochloride (d-meth.HCl) for 30 days, for a total of 25 or 50 mg/kg/per day. Values reported are group means expressed as ug/g tissue ± standard error of the mean. Rats were killed two weeks after the last injection. DA = dopamine; NE = norepinephrine. Wagner, G.C., Seiden, L.S., Schuster, C.R., *Drug and Alcohol Depend. 4*, 435-438, 1979.

Table 4

Effect of Methamphetamine on Regional Brain Catecholamine Levels in Guinea Pigs

Treatment	*N*	*Caudate*	*Telen-cephalon*	*Midbrain*	*Pons-medulla*
		DA	*NE*	*NE*	*NE*
Vehicle	4	9.63 ±0.27	0.33 ±0.03	0.50 ±0.10	0.30 ±0.02
d-Meth.HCl	6	4.83 ±0.66	0.33 ±0.03	0.42 ±0.08	0.35 ±0.05

Guinea pigs received methamphetamine hydrochloride (d-meth.HCl) subcutaneously at a dose of 6-30 mg/kg/day for 30 days. Values reported are group means expressed as ug/g tissue ± standard error of the mean. Guinea pigs were killed 2 weeks after the last injection. DA = dopamine; NE = norepinephrine. Wagner, G.C., Seiden, L.S., Schuster, C.R., *Drug and Alcohol Depend. 4*, 435-438, 1979.

terminals might be degenerating, but decreased storage and/or synthesis could account for the depletions. Schmidt and Gibb (1982) and Hotchkiss and Gibb (1980) found lower total activity of both tryptophan hydroxylase and tyrosine hydroxylase in rats and mice that had received high doses of AMPH or MA than in control animals. These two enzymes are rate-limiting for 5HT or NE and DA synthesis and the decreased synthetic rate could account for the decrease in steady-state levels. However, these enzyme kinetics are also consistent with cell or terminal loss. Ellison et al. (1978) provided morphological evidence for degeneration in rat brain. After prolonged administration of AMPH through slow release pellets, evidence of malformed cells appeared in the striatum. The potency of the toxic effect is measured by considering the behaviorally affected dose (B) relative to the toxic dose (T). Thus, T/B could be considered as the toxic index. With MA, T/B is 50-100, but with other compounds to be discussed below T/B is 2-4.

We found that methylphenidate, a drug functionally similar to AMPH and MA, did not cause changes in DA, NE or 5HT systems in rat brain. Therefore, not every anorectic psychomotor stimulant drug produces toxic effects to DA and 5HT nerve endings. In the past 5 years we have shown that a number of drugs, including AMPH, cathinone, 3,4-methylenedioxyamphetamine (MDA), mazindol, phenylpropanolamine, fenfluramine, and diethylpropion, affect the DA, NE and/or 5HT transmitter systems. Some of the drugs are toxic at doses which are outside the human dose range. Mazindol caused small depletions of NE at doses which were several hundred times the ED50 for the suppression of milk intake, but fenfluramine caused depletion of 5HT at a dose that was very close to the ED50 for the suppression of milk intake. Thus, based on the animal studies, one might conclude that the therapeutic ratio for mazindol was large but that the ratio for fenfluramine was small.

MDA has toxic effects on 5HT neurons in the striatum and the hippocampus of rats at doses of 3 to 6 mg/kg per day (Ricaurte et al., 1985). Even a single administration of MDA at a dose similar to that used by humans self-administering the drug has long-term effects on hippocampal 5HT. In general, drugs having structural and functional features in common with AMPH and MA have toxic effects upon related fiber systems within the CNS.

MDMA is another hallucinogenic amphetamine analog which appears to possess 5HT neurotoxic activity (Woolverton, 1986). One striking feature about both MDA and MDMA is that they produce very large 5HT deficits at much lower doses than MA (Ricaurte et al., 1985; Virus et al., 1986). Another is that neither MDA or MDMA produce DA neurotoxicity at low doses. Thus, substitution on the phenyl ring alters the spectrum of toxic actions of the amphetamine molecule and greatly enhances its 5HT neurotoxic activity. Another ring substituted amphetamine that appears to possess potent 5HT neurotoxic activity is fenfluramine (Commins and Seiden, 1986; Harvey and McMaster, 1977). Fenfluramine is currently used in the treatment of autistic children and efforts need to be directed at determining whether or not similar toxicity occurs in humans. The toxic potential of the ring-substituted amphetamines used or abused by man also needs to be evaluated.

Using kinetic analysis of DA reuptake, we have found that the number of reuptake sites was reduced by 50% by MA treatment. The affinity of the carrier system remained unchanged. In these experiments rats received MA for a period of 30 days. They were subsequently drug-free for a period

of 2 to 3 weeks prior to sacrifice. The synaptosomes were incubated with a buffered medium and varying concentrations of ^{3}H-DA (Snyder and Coyle, 1969). The kinetic constants Vmax and Km were determined by fitting the data to a rectangular hyperbola and doing double reciprocal analysis on the best fitting rectangular hyperbola. An approximate K_m value of 12 x 10^{-1}uM was found in both the control and the MA-treated animals. In contrast, Vmax expressed in disintegrations per minute was 7.9 x 10^{3} for control animals and 5.4 x 10^{3} for MA-treated animals indicating a loss of DA uptake sites (Fig. 1). We examined the number of high-affinity dopaminergic binding sites using ^{3}H-spiroperidol and found no difference in either the affinity or the number of binding sites (Table 5, Ricaurte et al., 1980).

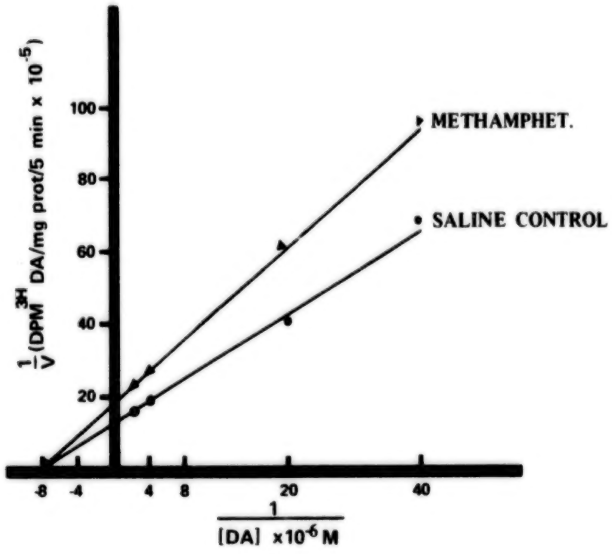

Figure 1. Double-reciprocal plot of ^{3}H-dopamine uptake by rat striatal homogenates 2-3 weeks after the high dose methamphetamine treatment (50 mg/kg per day for 4 days). Dopamine uptake was determined at dopamine concentrations ranging from 0.25 to 5.0 uM. The Km values of saline-treated (1.11 uM) and methamphetamine-treated (0.18 uM) were not significantly different. The difference in dopamine uptake site density (Vmax) is significant ($P<0.05$). Data are from one representative experiment replicated twice. Wagner, G.C., Ricaurte, G.A., Seiden, L.S., Schuster, C.R., Miller. R.J. and Westley, J., *Brain Res. 181*, 151-160, 1980.

Repeated high doses of MA also produce long-lasting depletions of 5HT in the rat brain. Within the 5HT system levels are reduced in the amygdala, frontal cortex, and striatum. It should be noted that the regional pattern of reduced 5HT levels after administering MA is similar to that seen after p-chloroamphetamine, the loss of 5HT synaptosomal reuptake sites occurs in much the same way as does the loss of dopaminergic uptake sites. Again, this evidence is consistent with the hypothesis that the nerve terminals are degenerating (Ricaurte et al., 1980).

Following chronic high doses of MA, levels of DA and 5HT are reduced for a prolonged period of time. The rate limiting enzyme for synthesis is proportionately reduced, and the number of uptake sites is also proportionately reduced. These observations are consistent with the hypothesis that the nerve terminals degenerate but confirmation requires morphological evidence of neuronal degeneration.

We now have evidence that striatal nerve terminals degenerate in rats after a single high dose of MA. Since a single dose produced toxicity, it was possible to check different time points using the silver impregnation technique to measure nerve terminal degeneration. The Fink and Heimer (1967) method depends upon the cell being stained with silver during the period of degeneration. Since the period of degeneration can be relatively short, it is necessary to do multiple time samples to find the correct period. The rats were killed 2 days after drug treatment since we had found from preliminary studies that the

Table 5

Specific Binding of ^{3}H-Spiroperidol to Striatal Membranes Obtained from Rats

Post-drug Period (weeks)	*Treatment*	*B_{max}(fmol/ mg prot.)*	*K_d(nM)*
2	saline	92 ±8	0.24 ±0.02
	meth.	107 ±11	0.19 ±0.03
4	saline	127 ±9	0.19 ±0.04
	meth.	116 ±6	0.22 ±0.03
8	saline	107 ±12	0.21 ±0.02
	meth.	102 ±14	0.23 ±0.04

Rats were treated with either 100 mg/kg/day of methamphetamine or saline for 4 days. They were killed 2, 4, or 8 weeks after the last injection. K_d and B_{max} values were derived from Scatchard analyses of specific ^{3}H-spiroperidol binding at concentrations ranging from 0.15 to 2.4 nM. None of the differences in dissociation constants (K_d) or receptor densities (B_{max}) between saline-treated and methamphetamine-treated rats were significant. Each of the values shown is the mean ± S.E.M. of 3 separate determinations. Wagner, G.C., Ricaurte, G.A., Schuster, C.R., Seiden, L.S., Miller, R.J. and Westley, J., *Brain Res. 181*, 151-160, 1980.

silver impregnation of degenerating rat nigrostriatal DA terminals is best achieved after a 2-day survival period (Figs 2 and 3). The results clearly show degeneration in the striatum suggesting that the DA fibers are degenerating. Since it was possible to block degeneration of 5HT fibers by pretreating with amfonelic acid, we were relatively certain that the observed degenerating fibers contained DA. We were also able to see degeneration in the hippocampus where there are very few DA fibers. In addition, we found massive degenerating pyramidal cells in the sensory motor cortex. The chemical transmitter in these cells is unknown at the present time, but it is of considerable interest that we find degeneration in this sensory motor area of the cortex. Chronic MA users often have sensory motor abnormalities which result in lesions to the skin from excessive scratching and picking. Whether this is related to the degeneration of pyramidal cells is as yet unknown.

Alpha-methyltyrosine (AMT) attenuates the neurochemical changes induced by MA, but reserpine enhances these changes. These differential results imply that the action of MA on the cytoplasmic transmitter pool may be responsible for the MA-induced neuronal damage. AMT reduces the cytoplasmic transmitter pool through synthesis inhibition whereas reserpine increases the cytoplasmic pool through destruction of the transmitter storage vesicles. It has been suggested that MA preferentially releases these cytoplasmic transmitters by reversing the direction of the high-affinity transport pump (Raiteri et al., 1979). The reserpine and AMT evidence supports the

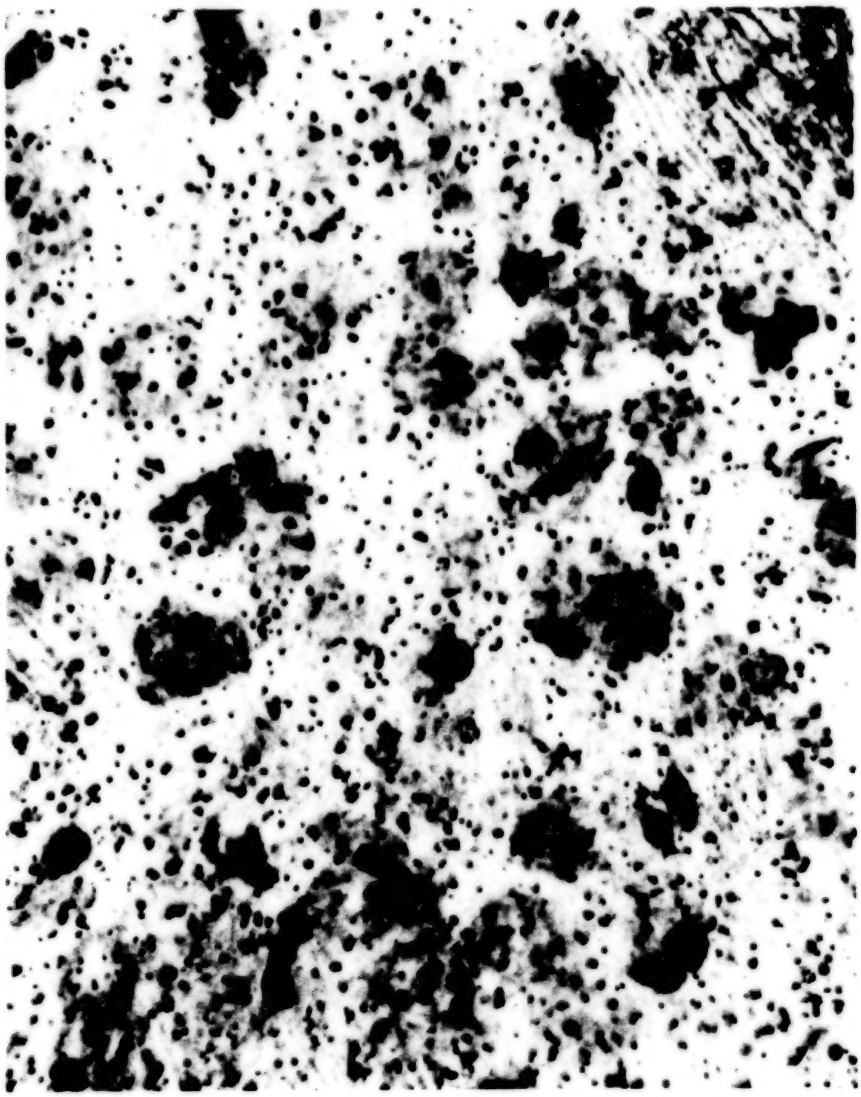

Figure 2. Fine granular degeneration in the rat neostriatum following the high dose (50 mg/kg) regimen of methamphetamine. Four-day survival period. Fink-Heimer method I with cresyl violet counter-stain x 1190. Ricaurte, G.A., Guillery, R.W., Seiden, L.S., Schuster, C.R. and Moore, R.Y., *Brain Res. 235*, 93-103, 1982.

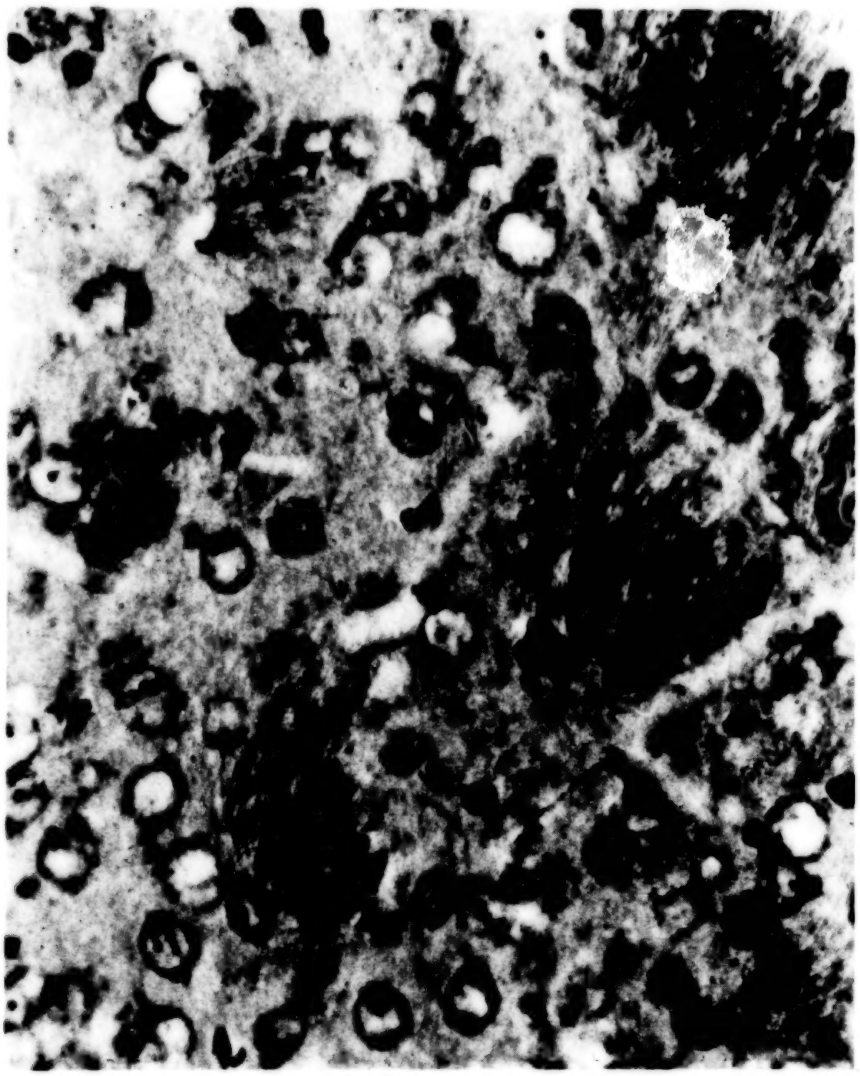

Figure 3. Absence of fine granular degeneration in the neostriatum of a rat treated with saline and killed after a 4-day survival period. Fink-Heimer method I with cresyl violet counter-stain x 1190. Ricaurte, G.A., Guillery, R.W., Seiden, L.S., Schuster, C.R. and Moore, R.Y., *Brain Res.* *235*, 93-103, 1982.

notion that the MA-induced toxicity is dependent upon this massive release of cytoplasmic DA stores.

Senoh and Witkop (1959) and Senoh et al. (1959) showed that DA could be non-enzymatically converted to trihydroxyphenethylamines such as 2,4,5-trihydroxyphenethylamine (6-hydroxydopamine, 6-OHDA). If DA is released by MA, and MA also blocks both DA reuptake and monoamine oxidase (MAO), the amount of DA in the synaptic cleft would be large, and an oxidative reaction could occur. To test this hypothesis, male rats were injected with 100 mg/kg of MA and then sacrificed after a time interval of either 20 minutes, 30 minutes, 1,2,4,8,16, or 24 hours. We found that between 30 minutes and 2 hours, 6-OHDA was formed in the caudate nucleus. The 6-OHDA amounted to approximately 5% of the DA that was present. The declining levels of dihydroxyphenylacetic acid (DOPAC) in the caudate nucleus indicated that the MA was a strong MAO inhibitor at this dose (Table 6). In addition, we injected 6-OHDA intraventricularly which causes about the same level of depletion of DA as the dose of MA that we used, and found that the levels of 6-OHDA were at least roughly comparable to the levels of 6-OHDA formed after MA. Further experimentation showed that the AMT attenuates the effects of MA and we, therefore, reasoned that AMT could prevent the formation of 6-OHDA. This hypothesis was confirmed (see Fig. 4).

In summary, we have shown that MA is toxic to DA and 5HT fibers in the central nervous system and that this toxic response is manifested by degeneration of nerve terminals. Furthermore, the toxicity to the DA system is mediated by DA itself which is oxidized to 6-OHDA due to increased release from the vesicles and blockade of inactivation. Whether this conversion of DA to 6-OHDA *in vivo* is a normal metabolic pathway that can occur in the absence of a drug, is certainly an interesting question and one that needs to be pursued. Several diseases, including Parkinson's disease and Huntington's chorea, are marked by the degeneration of the dopaminergic system. Whether a toxic metabolite of DA is responsible for these results is a question that remains open, but certainly in light of the data that we have presented, it is a reasonable possibility.

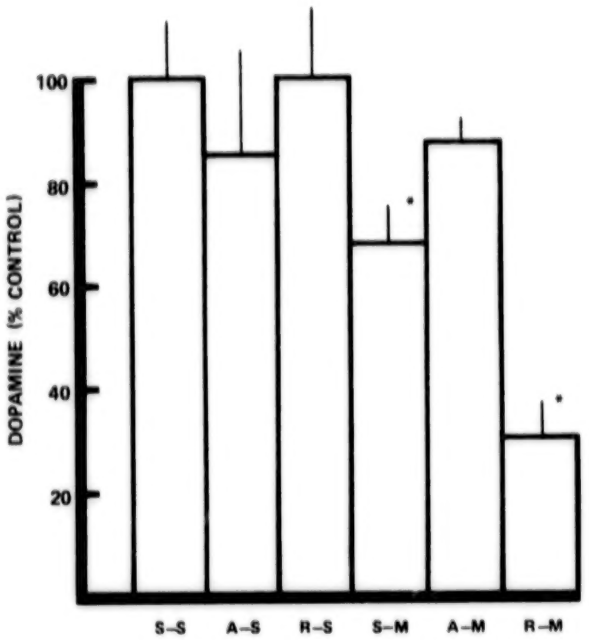

Figure 4. Caudate dopamine levels for 6 groups of rats treated with methamphetamine (M) (100 mg/kg each day for 4 days) or with saline (S) (2 ml/kg for 4 days). Reserpine (R), alphamethyltyrosine (A), or saline (S) were administered as pretreatment agents (see text). * = Significantly different from S-S group. Wagner, G.C., Locot, J.B., Schuster, C.R. and Seiden, L.S., *Brain Res. 270*, 285-288, 1983.

Table 6

Levels of 6-OHDA and DOPAC in Rats
Treated with 100 mg/kg Methamphetamine

Treatment	*Time of Kill Post Injection*	*6-OHDA* <----	*DA* *ng/mg tissue*	*DOPAC* ---->	*DOPAC/DA Ratio*
Saline	20 minutes	0	8.1	0.87	10.6
N = 8		0	(0.25)	(0.09)	
Meth.	30 minutes	0.20	8.7	0.72	10.2
N = 8		(0.17)	(0.68)	(0.07)	
Meth.	1 hour	0.39	6.1	0.62	8.3
N = 5		(0.31)	(0.60)	(0.07)	
Meth.	2 hour	0.24	6.4	0.44	6.8
N = 6		(0.21)	(0.84)	(0.56)	
Meth.	4 hour	0	5.7	0.37	6.4
N = 5		0	(0.65)	(0.08)	
Meth.	8 hour	0	6.9	0.33	4.8
N = 6		0	(0.54)	(0.04)	
Meth.	16 hour	0	6.3	0.78	12.4
N = 4		0	(2.6)	(0.25)	
Meth.	24 hour	0	4.1	0.77	18.8
N = 10		0	(1.2)	(0.29)	

(number in parentheses represent S.E.M.)

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THE EPIDEMIOLOGY OF MEPERIDINE ANALOG ABUSE

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Introduction

This paper provides a preliminary summary of epidemiologic investigations into the distribution of meperidine analogs (MAs) in the United States. It outlines the difficulties in detecting these compounds in street drug and autopsy samples, as well as in performing surveillance for them at the national level. These insights may be useful in designing public health and law enforcement programs to detect controlled substance analogs (CSAs) and to prevent adverse health effects produced by toxic CSAs and other similar drugs.

Since the discovery of the use and distribution of meperidine analogs (MAs) (Davis et al., 1979; Langston, 1983), there has been a great deal of interest in determining the extent to which these heroin substitutes have been available to narcotics abusers. It almost goes without saying that this interest is motivated by the fear that the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and other potential neurotoxins produced during syntheses of MAs may cause a future epidemic of parkinsonism.

The current approach to surveillance for narcotics worldwide is to rely upon a combination of data routinely collected by: medical examiners or coroners during forensic investigations of fatal overdoses; hospital laboratory analyses of samples from drug overdose victims; and law enforcement agencies through the analysis of samples of street drugs obtained during enforcement and intelligence operations. Data from these sources have traditionally provided a satisfactory assessment of the easily identifiable drugs that are abused at the local, state, and national levels. However, these sources can not assess the availability of drugs that could easily be misidentified, not detected by insensitive techniques, or are not present in autopsy samples.

The determination of the availability of MAs is hampered by each of these potential shortcomings. Meperidine analogs have been mistaken for meperidine, fentanyls, and have been missed by conventional analytic techniques. They also may not be identified if they are present in a mixture of drugs containing a known controlled substance such as heroin or cocaine, as most traditional algorithms for drug analysis employ simple screening techniques backed by extensive confirmatory analysis only for those controlled substances detected by screening. Likewise, discussions with MA users and former distributors indicated that fatal overdose is not usually produced by these drugs.

Current Surveillance

The absence of reliable surveillance data has led to the development of an alternative strategy that employs the

Table 1

Sentinel Symptoms Produced Soon After Exposure to Meperidine Analogs

Severe burning in vein	Blurred vision
Metallic or medicinal taste in mouth	Shaking or tremors
Jerking of limbs	Bradykinesia
Tightness, stiffness, aching or freezing of muscles	Difficulty speaking
Problems with balance or coordination	Difficulty swallowing
Numbness of extremities	Drooling
Loss of facial expression	Hallucinations
Increased oiliness of skin	Excessive sweating
	Difficulty opening eyes

collection and analysis of epidemiologic data and the use of an analytical laboratory with experience in measuring MAs in street drugs and biologic samples. Although MAs could have been distributed throughout the United States as well as in other countries, but because federal and state governments do not have the resources to look for MAs in every community, we have limited our investigations to those areas in which there is a strong suspicion of MA availability. In the past we have required either the positive identification of an MA in a street drug sample or the diagnosis of parkinsonism in a narcotics user.

In our investigations of the possible availability of MAs in specific communities, we have relied upon a screening interview that focuses upon the acute symptoms reported after injection of preparations of MPPP/MPTP by narcotics users in California (Ruttenber, 1986). MPPP is 1-methyl-4-phenyl-4-propionoxypiperidine, a meperidine analog sold on the street as "synthetic heroin." The symptoms noted by the users of this mixture were distinctly different from those produced either by heroin or by fentanyl analogs. The interview is initiated by asking if a person has ever injected a drug that has produced effects noticeably different from those usually produced by heroin, by fentanyl analogs, or by other common street narcotics. If the answer is yes, we then ask if this drug has ever produced any of the sentinel symptoms listed in Table 1. If the interviewee identifies two or more of these symptoms to be noticeably different from the effects produced by other common narcotics, then he/she is suspected of having used an MA.

Our investigations have been initiated in cooperation with state health departments and drug abuse treatment programs, which have provided access to clients under treatment for addiction to narcotics. The interview process is usually begun in these clinics because the clients are usually cooperative. Other appropriate groups of narcotics users are interviewed when possible. In conjunction with field interviews, we make attempts to obtain samples of street drugs and submit them to a laboratory with the capability of identifying MAs using gas chromatography/mass spectroscopy. These samples are obtained from law enforcement agencies after discussions with narcotics agents and forensic chemists. We ask about detection of meperidine in street samples and about the frequency of samples found to contain no controlled substance,

as these factors are suspected to reflect MA availability.

We have also asked narcotics users to submit samples of drugs that have produced the sentinel acute symptoms to either the anonymous sample submission program at the Institute for Medical Research, San Jose, California, or to the S.P. Laboratory maintained by Up Front, Inc. of Miami, Florida. Narcotics users, drug treatment program staff, and hospital emergency service personnel are also notified about the possible availability of MAs and encouraged to submit urine samples for analysis from patients who have used a suspected MA within the past 24 hours.

Community Investigations

California

Through efforts described elsewhere (Ruttenber et al., 1986) we have identified 562 persons who have probably been exposed to an MA, 287 who have met our exposure criteria. In April 1985, we notified drug treatment centers and narcotics abusers throughout the state of California of the possible continued availability of MAs, and identified 25 persons who met our exposure criteria and had used a suspected MA sometime in 1985. We established an anonymous sample submission program at this time and are in the process of establishing a long-term clinical follow-up of a cohort of persons exposed to MAs. To date, only five samples of street drugs have been submitted and none contained an MA. Nine urine samples have been submitted, and none contained an MA or a plausable metabolite of an MA. In November 1984, samples of a new MA 1-(2-phenylethyl)-4-phenylacetoxy-piperidine (PEPAP), were seized by law enforcement agents in Alameda County from a person who was linked to the original manufacturers of MPPP/MPTP in 1982. Based upon these data, we have concluded that MAs have been produced and distributed between 1982 and 1985 and are likely to be produced in the future.

Detroit

In July 1985 the CDC was notified of a 54-year-old Detroit man who developed acute-onset parkinsonism after injecting heroin. This patient noted that the drug produced burning at the injection site and a metallic taste in his mouth. During the course of our investigation, we found evidence that the patient used phenothiazines extensively prior to admission. We could not establish whether the patient's symptoms were due to MA exposure, phenothiazine exposure, or to a combination of these drugs. Screening interviews were conducted in 8 of the 10 Detroit inner-city drug treatment clinics. Of the 255 clients initially interviewed, 75 (29%) met the MA exposure criteria. Ten urine samples were obtained from persons who suspected MA exposure and none showed evidence of MAs or their metabolites. Twenty-nine samples seized by the Detroit Police Department and found not to contain a controlled substance were tested for MAs. All were negative. Because we lacked substantive evidence of MA availability, we decided not to establish an anonymous sample submission program. During the course of this investigation, we did receive a report of a Detroit chemist who, in the early 1980's, made MAs and pressed the powdered product into tablets. In 1983, the Drug Enforcement Administration reported that meperidine was identified in counterfeit hydromorphone (Dilaudid) tablets (DEA, 1985). It is possible that other such tablets could have contained MPPP/MPTP. From this investigation we could not substantiate current availability of MAs but we also could not rule out this possibility.

Florida

In October 1985, five gelatin capsules containing almost pure MPTP were confiscated from a Fort Lauderdale resident during a traffic arrest. The capsules were reportedly obtained from a street dealer who sold them as Dilaudid (hydromorphone). Preliminary discussions with drug treatment center personnel and clients confirmed that both heroin and cocaine street preparations are often sold in small gelatin capsules and that heroin users had, in the past months, noticed atypical effects. We interviewed clients in four methadone maintenance programs between Miami and Pompano Beach and talked with counselors, medical staff, and patients at a number of other drug treatment programs and hospital emergency rooms.

Forty-three intravenous drug users reported using a drug sold as heroin that produced two or more of the MA sentinel symptoms. Many of this group noted chronic symptoms similar to those reported by California MA users. Eight of the 43 had abnormal neurologic findings consistent with early parkinsonism. One 38 year-old white male who bought heroin in Miami between September 1985 and February 1986 was diagnosed with parkinsonism. In addition, 7 cocaine users reported experiencing two or more of the MA sentinel symptoms and 3 had abnormal neurologic findings consistent with multiple aseptic abscesses and ulcers that seem to be associated with the preparations that produced the sentinel symptoms.

A warning of possible MA availability was issued to drug treatment centers through the State of Florida Department of Health and Rehabilitative Services. Warnings were also made through South Florida news media. Persons who used a drug sold as heroin or cocaine and who noted any of the sentinel symptoms were encouraged to send samples of the drug producing such symptoms to the S.P. Laboratory anonymous sample submission program. Only four samples were submitted and none contained an MA.

Discussion and Recommendation

Our investigations in California and Florida strongly suggest that MAs have been produced and distributed in many U.S. cities between 1982 and the present. It also appears that MAs have been sold as cocaine, or used as a psychoactive diluent in cocaine street preparations.

Each of our investigations has highlighted the difficulty in proving the availability of MAs to drug abusers. Though clinical and intelligence data may strongly suggest the presence of these drugs, proof is ultimately based upon the recovery of a street drug sample containing the suspected substance. Our experience with anonymous sample submission programs has been discouraging. It is our impression that most drug users do not want to part with their drugs--no matter how small the quantity. Fear of reprisal or suspicion that the analytic results will never be provided may also influence this reluctance. We continue to support the availability of these programs, as they provide the only legitimate way to receive street drug samples and are too difficult to establish for emergency situations.

Because the standards for proof of drug availability are stringent, efforts should be directed toward continuous surveillance for all CSAs and new synthetic drugs of abuse. We recommend the development of a program to consistently obtain samples of synthetic drugs and perform extensive analyses on these samples. This program should include a number of U.S. cities and could be designed to target specific areas of potential CSA availability. Samples could also

be obtained from local law enforcement agencies that have noticed an atypical number of drug samples containing no controlled substances.

Our work in different cities and states has highlighted the lack of communications between drug treatment clinic personnel, emergency medical staff, law enforcement agencies, prisons, and State drug abuse prevention programs. We have found that drug abuse treatment clinics, prisons, and hospital emergency rooms are often the first places where drug abusers with medical complications of toxic CSAs are noticed. However, the personnel in these facilities are usually not aware of the signs and symptoms of toxic CSAs and do not know where to report these unusual medical problems. We recommend the development of communications networks at the State level to both train personnel and to encourage communications between facilities that provide services to drug abusers.

The CDC has recently received an appropriation from Congress to provide surveillance for and conduct research of the effects of CSAs. We will be working with the Institute for Medical Research and many Federal, State, and local agencies to cooperatively implement these recommendations.

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ECSTASY: PSYCHOLOGICAL CONSEQUENCES AND HEALTH RISKS

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"I've had some of the best times of my life on it," said a 22 year old senior from the University of Colorado, who called Ecstasy a "compassionate drug" which makes people "shamelessly mellow." A New York writer who tried it compared it to "a year of therapy in two hours." A Benedictine Monk from Big Sur said, "A monk spends his whole life cultivating the same awakened attitude it gives you."

Ecstasy, also known as Adam, or 3,4-methylenedioxymethamphetamine, its true name, was first developed in 1914. Its use in psychotherapy profoundly increased its popularity in the 1980's as a drug to enhance memory and curb anxiety in patients. Up until nearly a year ago its use was legal. It is now classified as a "Schedule I" controlled substance-the category for drugs with no accepted medical use and a high abuse potential.

Ecstasy is usually sold as a white powder, either loose or in capsules. There have been samples tested by Pharmchem Laboratories in California that were tan, beige or pale green. Prices ranged from $4.00 a cap in the 1960's to $25 or $30 today. The usual dosage is 100 milligrams. It is typically taken orally although undoubtedly there are those who have snorted it or taken it intravenously. It is said to taste very bitter if swallowed without the capsule but the onset of the drug's effects are much quicker. In Aspen, Colorado to combat the bitter taste it is often mixed with jello and known as "lick-em." It is sometimes mixed with juice as well. One hit's effect can last 4 to 16 hours.

In terms of validity, that is the extent to which the alleged content is the same as the actual composition, Pharmchem reports a 46% validity rate of MDMA sold as MDMA and containing exactly that. This is higher than that for methamphetamine (38%), amphetamine (11%), MDA (30%), but lower than that for cocaine (60%). The validity rate increases to 83% for alleged MDMA containing that substance but sold in combination with another substance. Chemically it is related to both amphetamine, a stimulant used for weight control, and mescaline, an hallucinogen.

It's effects have been described as making your body feel as if it were on Quaaludes (methaqualone) and your mind on a mild dosage of acid or LSD. Apparently, one feels this tremendous sense of being at one with the world and one's fellow humans. This probably accounts for its popularity among those who identify with the global consciousness and romantic ecology of the "New Age" movement.

Therapists familiar with its use feel that it helps people get in touch with feelings not ordinarily available and hence it is used to learn more about oneself and for personal growth. These feelings, at least by

some accounts, do not leave when the effects of the drug wear down. I spoke to two users of Ecstasy, both who had taken the drug for recreational purposes. Each reported that they have made significant changes in their life after consuming MDMA. One joined weight watchers and, eight months later, has lost over 40 pounds. The other entered psychotherapy to get her life in order.

On the other hand, however, Dr. David Smith, Director of the Haight-Ashbury Free Medical Clinic, reports that he is seeing some people in detox who have been taking 10 to 15 doses a day to reach an amphetamine-like high. Others, including Dr. Norman Zinberg of Harvard, states he has never seen "a single bad reaction" and it "has quite a low potential for abuse." This may well be true for most, but any mind altering substance such as MDMA has a possibility for abuse, particularly among youth and those in a precarious psychological state.

How widespread is the use of this drug? It is very difficult to arrive at drug use prevalence figures for any substance since illegal use is often hidden and drug abuse indicators are frought with complications. This is particularly true with MDMA.

The drug reportedly is manufactured in Berkeley, California, Cambridge, Massachusetts and Boulder, Colorado. On May 22, 1986 two Boulder residents were arrested on charges of delivering 2 ounces of MDMA to undercover officers. According to the DEA, the street value of this seizure was $4,500.

So it is known that the drug is available at least in Boulder. In fact, I called drug treatment directors around the state and was told conclusively that not only is it in Boulder, but also Denver, Aspen and Grand Junction. Yet, not one treatment admission was reported in any of these locations. The directors stated that most usage, according to their sources, is recreational. The types of individuals using it are not your "typical" drugee. They tend to fit more the stereotype of a "yuppie."

There have also been no admissions to the metro-Denver area hospital emergency rooms, at least according to the latest Drug Abuse Warning Network (DAWN) report for Denver. Nationally, however, there were 29 ER admissions during 1985, more than 3 times the number reported from 1977-1984. We are still deaing with a very small percentage of the total population and probably of the user population who are encountering difficulties with use of the drug.

What we do know can be summarized as follows:

1. Its users are advocates for the drug. This, considering the reported effects of use and the fact that users of anything generally support what they're using, is not suprising.

2. All things considered, few MDMA users are encountering difficulties with the drug. This is likely due to two factors: (1) it is typically used for recreational purposes, that is, to have fun, not because of a drug dependency or of filling of psychopathological needs; consequently, it is taken in fairly small dosages and not very frequently, and (2) and this is only a hypothesis based upon a limited sample, users appear to be relatively stable in their lives, they are not from low socioeconomic classes but more along the yuppie lines who want to experience more of the "me" generation.

3. Based on the few indicators available for this substance it appears

to be increasing in popularity and, consequently, prevalence.

4. It does have, as any mind altering chemical, a potential for abuse. This is manifested in the young and psychologically fragile.

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Public & Professional Education

Chairperson
Robert H. Feldkamp
Chief, Public Affairs Section
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Washington, D.C.

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PUBLIC AND PROFESSIONAL EDUCATION - FEDERAL PROGRAMS

Avraham Forman

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The National Institute on Drug Abuse has two major functions. One is to conduct and support research programs in the preclinical, clinical and prevention aspects of drug abuse. Our research activities in the area of designer drugs have been described by others at this conference. Our second functional area is informing professional communities and the public about drug abuse - in this case, about designer drugs.

Over the years we have had to inform the professional and general publics when individual analogs appeared and were identified by DEA and other law enforcement agencies. NIDA's Drug Abuse Warning Network (DAWN) and Community Correspondence Group have also produced information about the serious health consequences of the various designer drugs.

When such fentanyl analogs as "China White" became widely available in the late 1970's and early 1980's, our DAWN system documented emergency room visits and medical examiner mentions associated with the drug. NIDA's Division of Community Assistance disseminated information about the problem to State drug abuse agencies and facilitated information-sharing among those searching for solutions.

In 1984 we became involved in informing the professional drug abuse community and other health professionals about MPTP. NIDA staff reported the dangers of MPTP in a *Morbidity and Mortality Weekly Report* (MMWR) article which served later that year as the basis for an article in the *Journal of the American Medical Association* (JAMA). Because of its wide distribution in the medical community - particularly to poison control centers, emergency rooms, and medical examiners - this article continues to prompt frequent questions about MPTP from physicians around the country to Dr. Dorynne Czechowicz at NIDA. We also joined with other Public Health Service (PHS) agencies to sponsor a 2-day symposium on MPTP, involving representatives of health professional organizations to hear scientists from several countries present findings on the toxicity, clinical pathology, and epidemiology of MPTP. This, in turn, helped spark other research into MPTP.

Much of what we have learned about the adverse health effects of MDMA was based on studies supported by NIDA, and our research data and activities were instrumental in the emergency scheduling of MDMA in 1985.

One method of informing the general public and even some of the professional/policy-making community is through the press. In 1985 NIDA conducted a Science Press Seminar at which science reporters heard NIDA sponsored researchers report on the neurotoxicity of MDMA. At the same time, a NIDA Capsule (or fact sheet) on MDMA was prepared for members of

the popular press (newspapers, magazines, electronic media), sparking informative reports to the general public. This capsule has been updated to include our latest knowledge. NIDA staff also prepared an MDMA alert to the medical community, which was published in JAMA. NIDA has used ongoing programmatic approaches to inform professional communities about the dangers of designer drugs. *NIDA Notes* is a periodical publication mailed to all drug abuse treatment programs, prevention programs, State agency directors, and State prevention coordinators. The December 1985 edition contained an informative article on designer drugs and identified Dr. Czechowicz as a staff contact for further information and technical assistance.

We also maintain a repository of prevention information which is made available to State and community-based programs, parents' groups, and other national prevention networks. This repository contains information on designer drugs. A prevention oriented publication on designer drugs in now in preparation.

Our continuing work with health professions organizations has provided opportunities to affect their awareness and knowledge of designer drugs. We have worked with the American Psychiatric Association (APA) to develop policy statements about the clinical use of drugs which have not yet been tested for safety and efficacy, as a way of countering the use of MDMA by psychiatrists.

NIDA currently helps fund contracts with health professions and educational associations to identify products, approaches and educational strategies at all levels of professional education which can increase awareness and intervention skills of primary care givers. These include the American Nurses Association, American College of Obstetrics and Gynecology, Amercian Psychiatric Association, Ambulatory Pediatrics Association, and others. The subject of designer drugs should have a place in these projects.

Although NIDA has limited staff capability, we have provided technical assistance to a number of organizations which have tried to address designer drug identification and intervention. These include the American Academies of Pediatrics and Child Psychiatry, the Mobil Oil Corporation medical department and the State of Florida.

Our recently launched cocaine prevention media campaign is targeted at young adults who may be using or are at risk of using cocaine. The first phase of the campaign is off to a very successful start with television, radio and print ads to which our targeted audiences respond. We intend to expand the marketing of the campaign to college students later this year by reaching out to student organizations, campus newspapers and counseling services with our cocaine prevention materials. This activity might also provide a natural opportunity to disseminate information about the dangers associated with MDMA, which we think is popular on college campuses.

DESIGNER DRUGS

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Since the earliest recorded history, there has been no lack of accounts of the use of alcohol or other substances to produce an altered mental or physical state, either in the user or by design in someone else.

The term "designer drugs" was coined by Gary Henderson, Ph.D., of the University of California, Davis. Early use of the term denoted attempts of chemists to make slight alterations in controlled drugs of abuse thereby changing them to uncontrolled legal drugs with effects similar to the original. The new drug could not be judged illegal. Consequently, the manufacture/distribution network would be free from criminal prosecution. Important examples are:

- China White (Alpha-Methylfentanyl and other fentanyl analogs -- Synthetic Heroin)

- MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine). (By-product of a failed attempt to produce pure MPPP).

First, let's look at the fentanyl family.

Fentanyl, a synthetic narcotic, was imported to the U.S. in 1968, trademarked "Sublimaze," as a surgical anesthetic. Its usefulness is unquestionable - now used in approximately 70% of major surgeries in this country. Over the last several years, fentanyl analogs have appeared on the illicit drug market as a heroin substitute, and fentanyl has been a central drug in the high-tech "Designer Drug" phenomenon.

In recent years, these fentanyl analogs have been widely distributed within California's heroin user community as high grade "China White" heroin. Because they need not be imported, thereby avoiding the associated risks and expense of avoiding detection, and are relatively inexpensive to synthesize, in comparison with the production costs for heroin, stable supplies of fentanyl analogs are more easily maintained, at lower cost, and at a higher profit.

When law enforcement increased activities directed against "China White" sales began to seriously threaten the supplies and illicit profits, the suppliers simply shifted to another analog. Knowing they had a good thing going financially, chemists and suppliers of alpha-methylfentanyl decided they'd rather switch. Enter at least ten new analogs with the predominant one being 3-methylfentanyl, and the possibility of synthesizing hundreds of different fentanyl analogs.

In the early days, law enforcement agencies were hamstrung because the new drugs (analogs) were legal. It comes as no surprise that those involved in illicit drug supply and distribution networks exploited the

situation. However, subsequent scheduling powers were invoked and the Drug Enforcement Administration moved quickly to control the abused analogs of fentanyl.

The scare factor in using one of the fentanyl analogs is that there is a wide variation in potency among them. They may be up to thousands of times more potent than morphine. An effective therapeutic dose of the more potent fentanyls is measured in micrograms. Since an ordinary postage stamp weighs about 60,000 micrograms, the potential for overdose is readily apparent.

On the street, drug users are the guinea pigs. There are no quality controls, no standards, no procedures to remove contaminants. To date, fentanyl analogs have been confirmed as the cause of death in over 100 overdose deaths in California. Fentanyl analogs can be so powerful that some of those who died did so with the needle still in the arm.

The fentanyl analog situation dramatically illustrates the concept of high technology applied to drug abuse. Unfortunately, the higher the concentration of drug produced, the higher the potential for deadly consequences. The users of designer drugs sometimes don't live to tell about it.

Indications were that fentanyl analog drug use became more and more wide spread in California and that this trend spread to other areas. At that time, considering the freedom from hazards and ability to stay ahead of the legislative and regulatory processes by rapidly changing to production of new drugs, it seems most likely that synthetic drug production will be the wave of the future.

And now what about MPTP?

An analog of meperidine (Demerol) which also contained the neuorotoxin MPTP has been sold as synthetic heroin in the San Jose, California area. Exposure to MPTP can cause permanent Parkinson's Disease symptoms by affecting a specific area of the brain. At least 150 persons in this area are known to be affected. There are probably many more victims who have not been identified.

MPTP is a legal (non-scheduled) chemical, used commercially by pharmaceutical companies in the manufacturing of other chemicals. Probably its production was a result of a careless chemical procedure to produce a pure meperidine analog (MPPP).

In humans and other primates MPTP is highly selective in its ability to damage or destroy cells of the substantia nigra, a group of black-stained cells near the base of the brain. These cells are effectively responsible for normal muscle movement. Without this substance neural responses between the brain and muscles breakdown, resulting in a number of manisfestations collectively identified as Parkinsonism:

* Rigidity (increased muscle tone)
* Fixed, blank facial stare
* Drooling
* Shuffling gait
* Etc.

It is believed that the substantia nigra slowly degenerates in all people as part of the normal aging process. Fortunately, however, only about 1% of the population over 60 years of age actually reaches the threshold of damage beyond which symptoms of Parkinsonism develop.

Exposure to MPTP by drug users can prematurely accelerate this natural aging process such that the Parkinson's threshold is not only crossed, but is crossed many years earlier than it otherwise would have been. The chances of developing Parkin-

sonism following MPTP use have not been calculated, but indications are that the 1% figure in the normal population would pale in comparison. There are still an unknown number of heroin users who injected MPTP in limited quantities but have not yet exhibited Parkinson's symptoms; researchers believe these symptoms will show up at anytime - a year from now, or ten years from now.

It has been estimated that upwards of 500 heroin users have used MPPP/MPTP. In addition to those already seen, several more come forward each month. Not only have these cases presented a drug abuse problem, but they have created a new public health problem with unresolved economic and financial ramifications. Each of the advanced cases will require long term medical care and probably frequent hospitalization. They will become severely disabled over time and have practically no hope of ever leading a "normal life."

Sale and use of of MPPP/MPTP first became known in 1982, and the effects of MPTP were confirmed by Dr. William Langston, Chief of Neurology at the Santa Clara Valley Medical Center. We believed that MPTP production was purely accidental and that purposeful production of it defied all logic, even for the illegal drug market. Nevertheless, there is no evidence that MPTP will not return to the street again. At the present time, street samples for laboratory analysis will continue in an effort to determine if MPTP or other designer drugs are back on the street.

Seldom if ever before have we been faced with a drug of such dramatic potential for terrible disability and costly public health consequences. I believe we face a continuing battle in the control of clandestine laboratories and the resultant disasters that will occur.

With the close cooperation of law enforcement, prevention and treatment agencies and the scientific community, we will provide a united front to the communities we serve and especially to those who wish to subvert the law.

This conference reflects a cooperative trend and my compliments are given to Gene Haislip, Deputy Assistant Administrator, Office of Diversion Control in the Drug Enforcement Administration, and Frank Sapienza, Chemist/Pharmacologist, in the DEA. To all our colleagues who work daily on the front line of drugs, I say "Thank You!."

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Identification & Detection

Chairperson
John W. Gunn, Jr.
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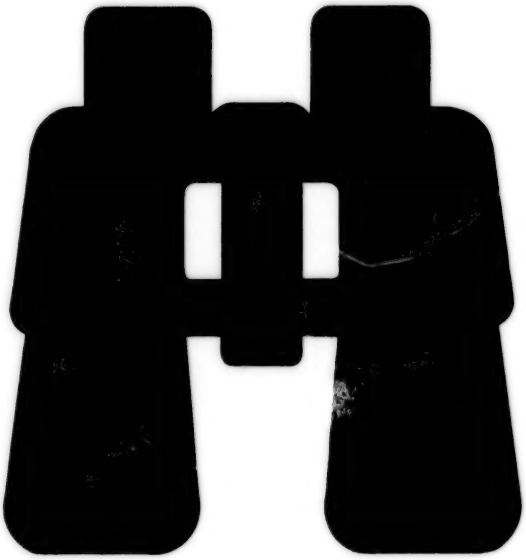

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INTRODUCTORY REMARKS REGARDING THE IDENTIFICATION AND DETECTION OF CONTROLLED SUBSTANCE ANALOGS

John W. Gunn, Jr.

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Twenty years ago, forensic chemists and toxicologists faced a new challenge -- what I call the "alphabet soup" of new drugs on the illegal market: LSD, DMT, DET, STP, etc.-- "designer drugs"/controlled substance analogs of the mid-1960's.

In the mid-1960's, there were about 85 police/crime laboratories in the United States. They were overwhelmed by this onslaught. Most laboratory staffs did not have the training, equipment, or an information exchange system to handle this new development.

Toxicology laboratories were scrambling for methodology to find LSD in body fluids.

Here we are in the mid-1980's with the *new* controlled substance analogs. However, I feel we are better prepared. We have over 250 crime laboratories. Most have trained drug chemists, good state of the art instrumentation, and information exchanges are in place through national and regional forensic society newsletters and, as always, through the informal system.

Toxicology solved the problem of LSD and has benefited from better trained practitioners, new instruments like the GC/MS, and new methodology. Professional toxicology societies, domestic and international, are better organized and membership has grown considerably.

As I said earlier, I believe we are better prepared to meet this new challenge. As one DEA chemist expressed it, "There has been a quantum jump in the state of the art in illegal drug chemistry. However, as it has happened before, quantum jumps in forensic analytical chemistry and toxicology have also been made."

After saying all that, it does not mean that we in the laboratories don't face problems, we do.

This morning we will hear from experts in toxicology and have views from both Federal and state laboratories. We will be looking at some of the special problems we face, such as:

New Methodology
Equipment
Training
Information Exchange
Safety Concerns

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DESIGNER DRUGS: THE NEW SYNTHETIC DRUGS OF ABUSE

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Today, new, totally synthetic drugs produced by clandestine laboratories are becoming an increasingly important source of abused substances. These illicit laboratories are developing new chemical entities from commonly available industrial chemicals and are distributing drugs which are selective in their pharmacological activity, very potent, and in many cases strictly legal.

THE ILLICIT FENTANYLS

Beginning in 1979, illicitly synthesized derivatives of fentanyl (Sublimaze^{R}) began appearing on the streets in California under the name "China White," the name usually associated with very pure Southeast Asian heroin.

To date at least 10 different fentanyl derivatives, in addition to fentanyl itself, have been identified. One of the newer derivatives 3-methylfentanyl is extremely potent (approximately 1000 times as potent as heroin) and is thought to be responsible for an alarming number of overdose deaths in California.

Physical Description

The fentanyl analogs are cut with large amounts of lactose, sucrose, or mannitol so the amount of active drug present is exceedingly small, less than 1%, and therefore does not contribute to the color, odor, or taste of the sample.

Color

The color ranges from pure white (sold as "Persian White") to light tan (sold as "China White", "Synthetic Heroin", or "Fentanyl") to light brown (sold as "Mexican Brown"). The brown color comes from the lactose which has been heated and has carmelized slightly.

Texture

The texture ranges from light and finely powdered to somewhat coarse, cakelike and crumbly, somewhat resembling powdered milk.

Odor

Occasional samples will have a medicinal or chemical odor, but this is not characteristic.

In summary, the fentanyls appear in all the various forms that heroin does and there is nothing characteristic about the appearance of any sample that will identify it as fentanyl.

Routes of Administration

Intravenous injection is the most common route of administration; however, the fentanyls are also smoked and snorted. Because of their high lipid solubility, the fentanyls should be excellent drugs for snorting and may become increasingly popular drugs among cocaine users.

Pharmacological Effects

Although the fentanyls are chemically quite distinct from other narcotics (morphine, heroin, methadone, etc.), they are pharmacologically equivalent. The fentanyls have all the effects, side effects and toxic effects of the classical narcotics. None of the illicit fentanyls have been given to human subjects under controlled conditions and virtually nothing is known about their detailed pharmacology and toxicology; however there have been literally hundreds of clinical studies on fentanyl and their results are summarized, very briefly, below. It is assumed that the effects of the various analogs will differ only quantitatively from the parent drug.

Euphoria

Heroin addicts perceive the "rush" and subsequent euphoria from fentanyl to be qualitatively similar to heroin and other narcotic analgesics.

Analgesia

Profound analgesia results with as little as 50 micrograms of fentanyl given intravenously. The euphoric effect may be achieved at even lower doses (a few micrograms).

Side Effects and Toxicity

Respiratory Depression

Respiratory depression is the most significant acute toxic effect of the fentanyls. The depth and duration of respiratory depression depend on the dose used and the analog used.

Bradycardia

Fentanyl produces a dose-dependent decrease in heart rate of up to 25% with a parallel drop in blood pressure of up to 20%. This is probably not a contributing factor in overdose deaths. However, when fentanyl is combined with cocaine ("speedballing") the myocardial depressant effects of both drugs should be at least additive and should be considered in overdose situations.

Chest Wall Rigidity

Chest wall rigidity, called "wooden chest" or "lead pipe rigidity," is a pharmacological response common to high doses of all narcotics and is observed with the fentanyls.

Antidote

Naloxone (Narcan^{R}) is the antidote of choice for respiratory depression induced by any of the fentanyls.

Addiction Liability

The fentanyls produce both tolerance and physiological dependence following repeated administration.

Pharmacokinetics

Fentanyl is very lipophilic and distributes from blood to body tissues very quickly. In fact, 10 minutes after IV administration, nearly all of a dose will have disappeared from the blood. Maximum brain concentrations are reached equally as fast, usually within 1 minute. This explains the very fast onset of action.

Fentanyl is rapidly metabolized and most of the drug is excreted as metabolites in both urine and feces within 24 hours.

Overdose Deaths

To date my laboratory has identified 106 overdose deaths caused by fentanyl or its analogs. Nearly all of these cases occurred in California; however two fentanyl deaths were identified in Oregon and one in Arizona which suggests that fentanyl

use may spread to other states. In fact in June of 1986 fentanyl analogs were seized in Florida. All overdose cases were similar in that they usually involved known addicts, injection sites and accompanying paraphernalia were found, and the autopsies showed the usual sign of narcotic overdose - pulmonary edema. Routine toxicological analysis of the body fluids revealed no narcotics, sedatives or stimulant drugs present; however, analysis of these fluids in my laboratory revealed very low levels (1 ng/ml or less) of the various fentanyl analogs. Fentanyl overdoses have occurred in nearly every major city in California, in suburban areas, and even in semi-rural areas. Ages of the victims ranged from 19-49 years and most (76%) were male. Also most (47%) of the victims were white followed by hispanics (26%) and blacks (25%).

THE FUTURE

It is this author's opinion that:

1. The domestic production of new, potent, synthetic drugs will be the major drug abuse problem of the future. As efforts to control natural products such as opium, coca, and marijuana become more successful, and as safeguards to prevent the diversion of pharmaceuticals become more effective, there will be more incentive to illicitly synthesize drugs within this country.

2. New synthetic drugs will appear which will be more potent and more selective in their action.

3. Smoking and "snorting" these drugs will become more popular because these routes of administration are convenient, effective, and use by these routes is difficult to detect.

4. The use of the new synthetics will spread beyond California to other states and perhaps to other countries.

5. The use of these drugs will spread to populations such as prisoners, parolees, medical personnel, and military personnel because of the low risk of detecting their use.

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LABORATORY PROBLEMS WITH THE CS ANALOGS (Abstract)

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Crime laboratories face major problems in analysis, clandestine laboratory investigation and in court presentations.

The major problems regarding controlled substance analogs are a lack of reference standard materials, a need for better methods for screening and positive identification, proper training and equipment for safety, and procedures for decontamination of areas exposed to the analogs.

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REMARKS PRESENTED TO THE CONTROLLED SUBSTANCE ANALOG LEADERSHIP CONFERENCE

Steven C. Helsley

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It is a pleasure to be here today. I'd like to thank Gene Haislip and Joe Krueger for all the work that went into setting up this conference. Once again California finds itself on the cutting edge of new drug abuse problems. While we were defending our borders from smugglers, a new domestic illicit drug production industry was born--clandestine laboratories and designer drugs. The law enforcement techniques required to address the problem are reasonably straight forward but the potential impact on forensic laboratories is great and we are not fully prepared to meet the challenge. For those of you who have not worked with me in the past, I should point out that I have spent almost 18 years in narcotic enforcement work, the last 5 and 1/2 years of which were as Chief of the California Bureau of Narcotic Enforcement (BNE). While I was in narcotic enforcement, I assumed that forensic laboratories were staffed with chemists and had specialized training that was readily available. Now that I do the hiring of criminalists for our crime laboratories, I find that my assumptions were unfounded. Our system and many, if not most, of the local police and sheriffs' crime laboratories are not necessarily staffed with chemists. In a full service forensic laboratory, chemistry is only one of the disciplines employed. Our staff does the analysis of body fluids, explosives, arson, firearms, and virtually any item at a crime scene.

Recently I hired a number of scientists one of whom had been studying impact craters on Mars with infrared and one who was testing wine for Gallo. Both were good scientists but neither was prepared to immediately assume the duties of a full fledged forensic scientist. This leads me to my second unfounded assumption and that regards training.

In California there is no academy or structured training program for forensic scientists. Our scientists promote and develop with the help of O.J.T. It has never been a good way to do business. It is becoming ever more serious a problem as the demands being placed on forensic scientists become greater. There is no source for training on clandestine labs and designer drugs.

California is serviced by 19 police and sheriffs' laboratories, 13 Bureau of Forensic Services (BFS) laboratories, and 2 DEA laboratories. Police and sheriffs' labs vary in size from 3 employees to 100. The BFS system has approximately 200. None of us are equipped to meet our training needs and many do not have the proper equipment to address the designer drug problem. What I would like to do today is to discuss four areas of particular concern and describe what we are doing to address them. The areas are workload problems, training, agency coordination, and safety.

The growth of the clandestine lab

industry has created a difficult workload problem for us. We are the primary source of forensic support for over 60% of California's law enforcement agencies. To that end, we provide criminalists, latent print analysts, and photographers to assist in laboratory investigations. Since January 1985, we have assisted at over 100 lab sites. The majority were methamphetamine labs, but we were also involved with PCP, MDA, cannabis, methaqualone, cocaine, P2P, and LSD labs. The average lab case consumes about 40 hours of a criminalist's time. Our principal client for lab cases, BNE, stands a very good chance of getting a substantial increase of special agents via AB 2692 this year. In that the new positions would be for lab investigations, we would expect an increased demand for our services. Concerns about safety and the need to train additional staff may cause us to adopt a standard operating procedure that calls for two criminalists to go to each clandestine lab scene. If we take this step, the increase to workload is obvious. In areas serviced by our smaller facilities, heavy clandestine lab enforcement efforts have put a real strain on our ability to provide a full range of timely services. Increased awareness about safety and the use of specialized equipment have also slowed the processing of crime scenes.

As I mentioned in my opening remarks, the police forensic scientist suffers from a lack of access to training. No where is that problem more acute than in respect to clandestine labs. Training needs include courses designed for narcotic enforcement officers and should discuss safety, analytical procedures, and lab takedown techniques. Currently I believe that we conduct the only clandestine lab course available for peace officers. That course is designed to develop the officer's expertise concerning methamphetamine and PCP manufacture for the purpose of obtaining search warrants. You will note that all my remarks are focused on the most frequently encountered drugs--not the so called "designer drugs." The reason is quite simple. We are struggling with basic problems concerning basic drugs. We are not prepared to deal with fentanyl, MPTP, and their ilk. It is quite possible that designer drugs are passing through our facilities in their street form undetected because we lack both the methodologies and awareness. My staff is very concerned about taking down operating labs and even more concerned about entering one that we strongly suspect is producing a more threatening substance. We have no reservoir of experience regarding designer drugs or the labs that produce them. Because the clandestine lab problem is relatively new and substances like fentanyl are so infrequently encountered, we are unsure what methodologies to employ.

To deal with the training problem, we are putting two plans in motion. In late July we are bringing together all of our staff who are involved in clandestine lab processing to discuss safety issues and sampling techniques as well as to share information on the formulas suspects were using to produce the drugs. From this gathering we expect to be able to produce technical guidelines which will bring more safety and standardization to our takedown procedures. It should also help us make better use of our instruments as this fall we will be taking delivery of state-of-the-art gas chromatograph/mass spectrometers, GC/MSD's, and micro-enhanced FTIR's, all of which will be used in clandestine lab analysis.

The second and most critical of our efforts is the attempt to create the California Criminalistics Institute (CCI). We, like all other forensic labs in California, must rely on the

FBI for training. What the FBI provides is good, but we can only send a total of ten students a year. Frequently the wait for a particular course can take several years. Senator John Seymour has introduced SB 2390 which would create and fund the CCI. Current plans call for a ten-thousand-square-foot facility adjacent to our headquarter's office that would eventually house a staff of twenty. The priorities will be set by an advisory board comprised of representatives from the California Association of Crime Laboratory Directors (CACLD), California Association of Criminalists (CAC), California Association of Toxicologists (CAT), California Division of the International Association for Identification (IAI), Drug Enforcement Administration (DEA), Federal Bureau of Investigation (FBI), Commission on Peace Officers' Standards and Training (POST), and myself as the chair. Based on preliminary discussions with those organizations, it appears that the four functions desired are training, application and methodology development, research, and advanced casework. The bill is moving through the Senate now and, of course, our hopes are great. If we are successful, the first CCI program will focus on clandestine laboratory training for forensic scientists and methodology and application development.

Four groups are involved with clandestine laboratories: law enforcement, forensic laboratories, fire fighters, and health agencies. If the problems caused by the drugs were not enough, the lab operators, with some degree of regularity, either burn or blow themselves up. They dispose of chemical by-products by dumping them in their backyard or in nearby streams or sewers. What results is that each clandestine lab must be considered as an extreme fire hazard and a toxic dump site. Firefighting agencies have been involved in the effort but agencies like the Department of Health and Human Services (DOHS) and Cal-OSHA are just beginning to see their role. We service approximately 400 police agencies. How many fire-fighting units they must coordinate with I have no idea. But I do know that radio communication alone is a serious problem. Coordinating takedown procedures is even more difficult. Frequently a small police or sheriff's department will walk in on an operating lab. It may be their first experience of that sort. We are called and, when we arrive and see what's going on, we may seriously disagree with the procedures being used. As our staff are not peace officers, it can sometimes be a difficult situation. In some parts of the State, DEA and BNE work all investigations together. In Fresno we have gone a step farther. My criminalists will not respond to a clandestine laboratory without a trained narcotic agent from BNE. Our experience thus far has been very good. I expect that more and more structured team relationships will be forged between state and federal scientists and narcotic agents. This will surely enhance effectiveness, efficiency, safety, and intelligence gathering.

The staff of health departments, both county and state as well as Cal-OSHA, can play an important role in these cases. After the scene has been processed and samples of chemicals taken, hundreds and sometimes thousands of gallons of toxic substances must be removed by licensed haulers. They can both arrange and pay for the hauling--which is extremely expensive. If dumping has occurred, they can tap the State superfund to clean it up. Both are also equipped with specialized equipment that we don't have which can monitor the environment at the site to determine the level of protective clothing which should be worn. We are in the process of discussions

with Cal-OSHA about the potential for them to respond with us to clandestine lab scenes. Much needs to be done as their command staff is not as attuned to this issue as we are. We feel positive that something can be worked out between the State agencies and we were pleased when DOHS presented a Hazard Assessment Response Program (HARP) class to our staff in May. We intend to take a lead role in bringing State agencies into a fully coordinated program.

The issue of safety is the most vexing. Think of the crime lab as the confluence point for decaying body parts and fluids, explosives, chemicals, radiation, and drugs. Frequently all are contained in too little space, often improperly ventilated and planned with instruments requiring compressed gases and huge amounts of electricity. Perhaps when we send our staff on field calls to take down drug labs, we are sending them to a safer environment. Last year, I asked our staff to update our safety manual and to put together a safety training course. The lead person in the effort, the manager of our Redding Laboratory who is a "can-do" person, couldn't do it. The safety problems of the forensic laboratory are much broader than what is created by drug labs. But we aren't prepared to deal with any of it. Research in this area is almost nonexistent. As we are experienced in this area as any, there is no one to turn to for help. We must do the work to solve the problem.

When our staff first began discussions on what we felt were safe practices, our most experienced people were 180° apart. After the HARP class which I described, our staff had their safety concerns increased by a factor of ten. A committee was formed of scientists, photographers, latent print analysts, and agents to work out some of the problems. Their first task was to select the proper safety equipment. That has been done and we are in the process of purchasing it. Next they will develop proposals for policy concerning the wearing of equipment and identifying the proper roles and procedures at the scene. When we complete this, we intend to share it with anyone who is interested. The hazards posed by chemicals used in producing drugs are described in material safety data sheets (MSDS). The information in the MSDS is produced by the companies that manufacture the chemicals. The finished product is also well understood--we understand what drugs like PCP can do. When our staff enters a lab, we usually must contend not with the precursor chemicals or the finished product alone, but intermediary materials which are unknowns. Our immediate response to these exposures is two fold. First, our staff will undergo baseline medical evaulations. The second aspect is the preparation of a HARP form which we designed that will 1) document the basis for the decision to initiate the "takedown," 2) document conditions and chemicals at the site; and 3) document episodes of chemical exposure reactions occuring during and after the processing. We believe that these measures are worthwhile but are not a solution. The entire issue of safety in the forensic laboratory needs to have research work done. We need to understand the risks from seizure through the lab evidence vaults, to the courts and, finally, to destruction. I posed these types of questions to both the FBI and the American Society of Crime Laboratory Directors (ASCLD). Both agreed that there was an urgent need but could not provide concrete assistance. In that I felt that the safety issue was the most pressing in the forensic community, I asked the lab directors from Arizona, Oregon, Nevada, and a group from California to jointly prepare a research safety grant proposal which was submitted to the

National Institute of Justice (NIJ) on April 18, 1986. The proposal requests $662,000 for 21 months of research into all aspects of forensic safety. The research would be done by consultants under the direction of our Bureau safety coordinator who we would donate to the effort. We have received excellent nationwide support for our proposal and expect a decision from NIJ soon. What we have proposed is critical and basic and has never been attempted before. Without it we can't solve our problems. President Harry Truman best described our predicament--"It's not hard to do right, it's hard to know what's right to do." I have copies of our grant proposal for anyone who is interested.

In conclusion, much work lies ahead of us to solve our training, safety, workload, and coordination problems. Without this work we will not be able to adequately address existing or emerging designer drug and clandestine laboratory problems.

It was a pleasure to have this opportunity to address you and I know that conferences such as this are an important aspect in problem solving.

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Law Enforcement Aspects

Chairperson
Raymond J. McKinnon
Chief, Dangerous Drugs Investigations Section
Drug Enforcement Administration
Washington, D.C.

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A LAW ENFORCEMENT PERSPECTIVE: "THE SPUTTERING FUSE"

Joseph E. Krueger

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San Francisco Field Division
Drug Enforcement Administration
San Francisco, California

At this juncture you have had the opportunity to examine several facets of the controlled substance analog problem, the attendant health risks, the ramifications of public education, and the difficulties of detection and analysis of these substances -- more commonly termed "designer drugs."

It is my purpose to briefly explore the law enforcement challenges presented by this phenomenon and at the same time raise some of the problems and possible solutions.

To provide a structure or foundation for my remarks, I would first like to share a perception which, while not scientifically validated, is an enforcement view of the present and future analog problems.

"Designer drugs" per se are not a new issue to law enforcement or most of you. In fact LSD may well have been one of our country's first such substances of abuse. The LSD epidemic of the early 70's which was born right here in northern California serves as an interesting parallel. What we had were a relatively few reasonably unsophisticated chemists, who, spurned by the hype of the times, produced a psychedelic substance (LSD) literally without any quality control or consistency of purity. This produced a rash of very bizarre behavior in LSD users, occasionally leading to serious injury and/or death. Together with the attendant media attention and public concerns these occurrences resulted in a significant waning of "acid" production and abuse. However, the last few years have shown a resurgence of LSD production and one of the many reasons for this increase is driven by the consumer. Admittedly, times and public attitude have changed and so have the abilities of the now sophisticated clandestine LSD chemists who are capable of producing a very consistent finished product (approximately 50 micrograms per dosage unit) for which the consumer can expect a predictable "trip"; one which is not life threatening and yet psychedelic in every sense of the word. I believe it is fair to equate these LSD production, distribution and consumption "swings" to the problems that the Chrysler Corporation faced necessitating Iococca's intervention to rekindle the record of quality control and dependability --- thus the consumer confidence apparently enjoyed by Chrysler Corporation today.

So too, I suspect that we will see similar swings and shifts with all variety of drug analogs. Clearly today we are seeing the finished product of a relatively few chemists who are capitalizing on "if you will" commercially patented analogs and the ability to produce a product, as is in the case of the fentanyls, extremely unpredictable insofar as

"street" purity.

Our experience to date would indicate considerable consumption of the analogs with unpredictable results, some resulting in deaths, at least in California, and a corresponding media and more recently public focus on the problem.

Perhaps one of the pervasive questions for this conference might well be -- is the drug analog problem a "sputtering fuse" - yet burning, awaiting a few excellent chemists to produce a quality product of consistent purity and without the attendant Parkinson's symptoms or overdose leading to death? I believe that that fuse is sputtering along, and not far from the real "black powder" which has every potential of significantly altering U.S. and possibly international drug abuse patterns.

Regrettably, California has established a leadership role in the illicit production of clandestine substances ranging from extremely high grade sensimilla to the clandestine manufacturing of all variety of drugs and the analogs. Presently there are literally hundreds of illicit laboratory operations throughout the state of California, most of which are producing a "poor man's cocaine" -- methamphetamine. We are also seeing a growing number of PCP laboratories, cocaine conversion laboratories, and yes a few fentanyl laboratory operations. This year the San Francisco Field Division of DEA will raid and dismantle approximately one (1) clandestine laboratory each week, and we can reasonably expect that the state and local law enforcement authorities throughout the state will ultimately remove something in excess of 100 illicit laboratories this year.

From the law enforcement perspective, the investigation of illicit laboratories is a terribly demanding, exceptionally dangerous and frankly downright unattractive pursuit. Controlled substance analog investigations are fraught with multiple additional difficulties, none of the least of which are the relatively insignificant, readily available precursors required to produce an extremely dangerous product which all too frequently is uncontrolled.

The DEA laboratory chief Robert K. Sager has estimated that for the paltry sum of $150.00 a chemist could produce in about 4 days 500 grams of 3-methylfentanyl. This is the equivalent of 50 million dosage units, which sold at the approximate street price of heroin would net a profit of something just short of $500 million dollars. That chemist by his nature, and based on our experience to date, will distribute this product through a very closely knit group of associates, most of which will be heretofore unknown to law enforcement and/or our intelligence systems.

I think you can readily see the profit motive and complexities of the problem facing law enforcement in the pursuit of the analog chemists and their organizations.

With the advent of analogs, we no longer enjoy many of the traditional drug law enforcement strategies heretofore associated with the cultivation of natural substances on foreign soil (poppy or cocoa). We forego the interdiction opportunities provided at our borders and ports, and have for the most part lost our traditional methodology of tracking essential precursors to the illicit laboratories. Thus the law enforcement community is nearly totally dependent on intelligence and cooperative sources to identify, target, and successfully apprehend the manufacturers of analog drugs.

Perhaps more difficult are the issues of agent and chemist safety in the

seizure and dismantling of analog laboratories. Many of these substances clearly produce unknown, yet potentially toxic, carcinogenic or other physiological consequences simply on exposure to the environment in which the product was being synthesized. Law enforcement faces a very real constraint in the ability of its analytical systems to accurately identify some of these analogs with absolute certainty. Finally, we have the very troublesome issue of seizing analogs which are not under control, or, if you will, technically legal.

The picture which I have presented is not very optimistic, fraught with many difficulties for the law enforcement community, and I think, destined to become an increasingly troublesome abuse problem with all the attendant health and social and economic consequences.

As the Drug Enforcement Administration and associated domestic and foreign law enforcement agencies continue to bring pressure on the production and distribution of the more traditional substances of abuse, I believe it inevitable that we will see a continually escalating domestic production of controlled substance analogs.

I do see the potential for success; however, success will absolutely necessitate a combination of legislative initiatives, aggressive law enforcement and equally important, public education, prevention and research initiatives.

DEA has mounted a number of successful controlled substance analog investigations resulting in the removal of illicit laboratories and controlling organizations. Noteworthy here in California was the 1985 Glen B. Perry/Kenneth Baker investigation, which resulted in the Federal arrest of several defendants, the seizure of considerable assets and multiple pounds of what were then several uncontrolled fentanyl analogs. I do not intend to detail that investigation except to say that all indications were that the defendants were very carefully producing analogs just beyond the reach of the Controlled Substances Act. Later in this conference, Assistant United States Attorney Brian Layton will discuss the prosecutorial ramifications of an analog case which was perfectly legal -- or so the defendants thought.

Particularly noteworthy is a March 1986 finding by Doctor Gary Henderson, University of California Davis, which reports that there have been no new California fentanyl deaths since August 1985. While in no way conclusive, we would like to believe that the Baker case and a few others may have significantly impacted on the current availability of fentanyl analogs.

Ladies and gentlemen, I have tried to characterize the magnitude and future of the designer drug problem, and at that the same time identify many of the handicaps which are facing the law enforcement community.

The issue of controlled substance analogs is a serious matter, not only for this generation, but as in the case of PCP contamination, the problem may well be passed on to future generations. Let me close by recommending several actions which are deserving of immediate attention.

First of all, the Federal and state legislative branches of our country need to recognize the magnitude of this problem and enact apporpriate legal devices such that the criminal justice system can deal effectively with the manufacturers and distributors of designer drugs. In the area of education, our public safety personnel, police, courts, correc-

tions and the general public must be made accurately aware of the health and safety problems associated with this phenomenon. With respect to environmental protection, our public health services must become involved with the entire issue of clandestine laboratories, including appropriate research as to what the effects of exposure to hazardous substances encountered in those laboratories have on the criminal justice personnel attempting to deal with them. In the private sector, chemical companies who distribute essential precursors used in the manufacture of illicit drugs must insist on full identification of all cash sales.

Further, possibly additional precursor chemicals should be brought under control. There are a variety of additional requirements in terms of safety equipment for law enforcement personnel, and in many cases additional trained law enforcement resources may be needed to combat this problem.

I appreciate the opportunity to join with you in examining the current and future ramifications of controlled substances analogs, and I eagerly await the findings and recommendations of this national conference.

Thank you very much.

HALLUCINOGENIC AMPHETAMINE INVESTIGATIONS

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Thank you very much for the kind invitation to address you on a problem that concerns all of us. It is indeed a pleasure for me to participate in this Conference on Controlled Substances Analogs, and in particular to share with you some information about the controlled substances analog MDMA or ECSTASY.

In early 1985, our intelligence indicated that several shipments each month of as many as 50,000 to 100,000 dosage units (tablets) of ECSTASY were coming into the Dallas area from somewhere in California. The tablets were being sold openly for $15 to $25 a tablet in many of the bars and clubs in Dallas. Credit cards were even being used to obtain ECSTASY and people were being recruited to become distributors of the substance. The abuse appeared to be especially prevalent in both the gay community and the college community.

For a period of time our office was receiving several calls a week from persons who had been approached to become ECSTASY distributors with the promise of making several hundred thousand dollars within a few months. They wanted to be sure that MDMA was not a controlled substance and that they could not be arrested for selling it. Apparently there was no concern for the health and safety of the people to whom they would sell the drug - they were interested only in the financial gain they could make prior to ECSTASY becoming a controlled substance. There was even a 28 page booklet entitled, ***ECSTASY: 21ST Century Entheogen***, being furnished to proposed distributors (and to some users) of this drug. This booklet represented ECSTASY in the most favorable terms and failed to mention the dangers that anyone takes when ingesting a drug which is clandestinely manufactured and which is used recreationally instead of under the supervision of a physician for a legitimate medical purpose.

Prior to ECSTASY (MDMA) being controlled, our agents in Dallas had purchased some of the tablets and submitted them to the DEA South Central Laboratory for analysis. As expected, the analysis confirmed that ECSTASY was MDMA (3,4-methylenedioxymethamphetamine). Partly because of the widespread use that was occurring in Dallas and on the West Coast, DEA used its emergency scheduling authority on May 31, 1985 to temporarily place MDMA (ECSTASY) in Schedule I of the Controlled Substances Act effective after July 1, 1985. As you are aware, the emergency temporary placement of MDMA into Schedule I was a completely separate and parallel action from the administrative scheduling process which had been underway since July 1984 to permanently schedule MDMA.[1]

As soon as ECSTASY became a Schedule I controlled substance, the Dallas

Office of DEA began to aggressively pursue those individuals who were engaged in the illegal trafficking of ECSTASY. But before I mention some of the specific investigations involving ECSTASY and some of the problems that occurred during these investigations, I want to tell you a little about what happened in the Dallas area just prior to ECSTASY becoming a controlled substance.

As ECSTASY (MDMA) had become a very popular recreational drug in Dallas, on the weekend before it was to become a controlled substance there were numerous ECSTASY celebrations at bars and parties. It was the last legal fling with ECSTASY before it became controlled. These parties were reported by most of the T.V. stations in Dallas on their nightly newscasts as well as the local newspapers. Life Magazine mentioned them in their August 1985 issue in a special report entitled, "The Trouble with Ecstasy."

Users of the drug were quoted as saying they were not worried about ECSTASY becoming controlled as they still would be able to buy it, but that they would just have to be more careful after it was a controlled substance. Other users said that the suppliers of ECSTASY had already created another non-controlled analog with similar properties and effects as ECSTASY. Both of these quotes have turned out to be true. ECSTASY is still widely available in the Dallas area and a non-controlled analog of ECSTASY called EVE is now being sold in the Dallas area. EVE is apparently 3,4-methylenedioxy-N-ethylamphetamine (MDE). Some users of EVE apparently say it isn't as good as ECSTASY as it isn't as strong and causes many users to throw up (vomit) when using it. Recent reports have indicated that ECSTASY is now becoming a favorite recreational drug in some of the high schools in the Dallas area.

To illustrate the availability of ECSTASY in the Dallas metroplex, I would like to highlight four cases which give an overview on the wholesale availability of ECSTASY in the Dallas-Fort Worth area.

Case 1

On July 29, 1985, the Dallas Field Division, in cooperation with the Dallas Police Department, the Irving Police Department and the FBI, arrested several individuals as they delivered 31,200 ECSTASY tablets in Dallas, Texas. Their source of supply was also arrested. Seized from him was a briefcase containing an additional 1,000 Ecstasy tablets plus organizational records of his MDMA (ECSTASY) distribution organization. A small amount of marijuana and cocaine were also found in the attache briefcase as was a realistic portable scanner that was to be used by the organization to monitor DEA's frequency.

During the undercover probe of this ECSTASY distribution organization, a DEA undercover agent had previously made three purchases of ECSTASY tablets (a total of 1,140 tablets).

The Dallas supplier of Ecstasy is believed to have obtained his tablets directly from the laboratory located in California and according to statements made at the arrest scene, was enroute to the Corpus Christi and Houston, Texas areas. Records held by this individual indicated that he was also a distributor in the Las Vegas, Nevada area.

Case 2

On September 30, 1985, agents from the Jackson, Mississippi Resident Office, Dallas Field Division, and officers of the Dallas Police Department arrested two individuals in Dallas, Texas as they were delivering 1,200 dosage units of ECSTASY (MDMA)

to an undercover agent from the Jackson, Mississippi Resident Office.

Case 3

On October 2, 1985, two individuals were arrested when they delivered approximately 2,800 dosage units of MDMA (ECSTASY) to Drug Enforcement Administration and Dallas Police Department undercover agents. (One of the arrestees was featured in August issue of Life Magazine promoting ECSTASY usage).

Negotiations and delivery of the controlled substance were a result of an arrest of two individuals and the seizure of 1,200 dosage units of MDMA (ECSTASY) the previous night.

Intelligence obtained prior to the two independent investigations indicated that Dallas is the national distribution center for MDMA (ECSTASY) and that the head of the organization was headquartered in Dallas, Texas.

Case 4

On December 7, 1985, two men were arrested at DFW airport when they delivered 820 dosage units of MDMA to a cooperating individual under the surveillance of special agents of the Dallas Field Division Office, Jackson Resident Office, Mississippi State Bureau of Narcotics and Dallas Police Department.

Our experience has shown that those people who manufacture analogs of controlled substances (designer drugs) will continue to produce new non-controlled analogs faster than DEA is able to place them in Schedule I under our emergency scheduling procedures. I believe it is imperative that the "Controlled Substance Analogs Enforcement Act of 1985" be passed by Congress as soon as possible in order for DEA to more effectively combat the increasing problem of analogs of controlled substances (designer drugs). I understand that this piece of legislation will be discussed by Steve Stone this afternoon so I won't say any more about it at this time.

It has been my pleasure to speak to you today.

[1]*Editor's Note: The DEA Administrator, in a Federal Register notice published on October 14, 1986, placed MDMA into Schedule I of the Controlled Substances Act on a permanent basis effective November 13, 1986.*

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CONTROLLED SUBSTANCE ANALOGS - A STATE LAW ENFORCEMENT OFFICER'S PERSPECTIVE

Robert S. Elsberg

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I would like to thank the U.S. Drug Enforcement Administration for allowing me to give this presentation and participate in the Controlled Substance Analog Leadership Conference.

Unfortunately, California has the distinction of leading the country in many areas of substance abuse. In the 1960's LSD was first seen and abused in California. Phencyclidine, "PCP" followed in the 1970's and Hayward, California became recognized as the "PCP" capital of the world. Today, Santa Clara and Los Angeles Counties, California fight for that distinction. When law enforcement tracked chemicals needed for the manufacture of "PCP", California began to see "PCP" analogs such as the morpholine, ethylamine, and pyrrolidine analogs. These analogs are derived by simply replacing the chemical (piperidine) watched by law enforcement with another chemical.

In the 1980's, California was first again with the introduction of designer drugs from the acetylfentanyl family of analgesics. These designer drugs were illicitly manufactured and sold as "China White," a name that up until then was exclusively recognized as a very potent form of heroin.

In 1985 California seized over 200 clandestine drug laboratories to become the leader in our country for such illegal productions. In the previous year, 1984, 90 clandestine laboratories were seized in California and that was considered, and is, a significant number of labs. With the number of laboratories seized this year to date, California will surely surpass its own record and again lead the nation in 1986.

This conference is intended to focus on designer drugs. What did California do about the "China White" phenomenon in the 1980's? China White was first described to California law enforcement statewide in 1981 in an article that appeared in a quarterly publication of the Western States Information Network (WSIN). WSIN is an intelligence network composed of California, Washington, Oregon, Nevada and Hawaii. WSIN collects and disseminates intelligence on controlled substances, substance traffickers, substances seen on the street, methods of substance concealment, etc. The article was titled Alpha-methylfentanyl and was authored by Dr. Gary Henderson of U.C. Davis. The article described alpha-methylfentanyl as 200 times stronger than morphine, appearing in Orange, Los Angeles, and Monterrey Counties. A substance 200 times stronger than morphine was unthinkable to law enforcement since most substances abused were so diluted, i.e. heroin, frequently three to five percent pure on the street, that just 100 percent morphine was considered extremely powerful. 200 times stronger than pure morphine just simply could not

be true.

When law enforcement first encountered "designer drugs" (China White) on the street, they assumed it was Asian Heroin. Time after time, law enforcement submitted these substances to the crime lab after purchasing them while working undercover and time after time law enforcement was told these substances were negative for controlled substances. Informants swore that these substances were "dope" and that they themselves had used it. Needless to say, law enforcement's relationship with these informants during this period of time was at best shaky.

At approximately the same time as WSIN published its article on alpha-methylfentanyl, the U.S. Drug Enforcement Administration (DEA) advised criminalistic laboratories throughout California that they could send these "China White" substances to Washington, D.C. where they had the equipment to test for the presence of alpha-methylfentanyl. Samples were submitted from local law enforcement throughout California to DEA and then sent to Washington, D.C. for analysis. At first, results came in rapidly but then a slow down occurred probably due to the number of submissions. As a result, law enforcement generally quit purchasing anything referred to as "China White." After all, not only was the criminalistic examination a problem of delay, but there was no state violation for possession or sales of alpha-methylfentanyl. It should be noted that Dr. Henderson in Davis, California also had the ability to test the substance, but he was only one additional resource.

1982, 1983 and 1984 saw the presence of para-fluorofentanyl and 3-methylfentanyl, other designer drugs in that same fentanyl family that were ***legal***.

In 1984 California Attorney General John K. Van De Kamp sponsored assembly bill 2401. AB 2401 authored by Dr. Bill Filante swiftly passed the legislature and became law in California. The entire acetyl fentanyl family of analgesics, literally hundreds of substances that in some cases were up to *10,000* times stronger than morphine, were controlled with the passage of this bill. This bill became a model for other states throughout the country to follow.

In 1985 both the Los Angeles Police Department and DEA seized fentanyl analog laboratories in Southern California. Since that day, law enforcement in California has seen relatively little, if any, designer drug substances on our streets.

Today, the DEA laboratories in California have the equipment to test for these substances.

Another designer drug that law enforcement encountered in California in the 1980's was N-ethylamphetamine. This substance is a substitute for methamphetamine, aka "speed." An important chemical (methylamine) watched by law enforcement and used in the manufacture of methamphetamine was replaced by another chemical (ethylamine) that was not watched and this produced the perfectly legal drug, N-ethylamphetamine.[1] Today, that previously unwatched chemical, ethylamine, is tracked, and N-ethylamphetamine is now non-existent in California.

What are we doing about the drug trafficking and production problem in California? Twenty years ago, the California Bureau of Narcotic Enforcement employed 100 special agents assigned throughout the state to work full time in tracking down and apprehending controlled substance traffickers. In those days, very few controlled substance laboratories

were seized and just one kilogram of cocaine was practically unheard of. Today, one kilogram of cocaine is so common a seizure that in some instances, it results in only a probationary sentence. Today, when over 200 clandestine laboratories are being seized in California, marijuana cultivation in California is at an all time high, the most potent form of designer drugs are appearing on our streets, and over 100 pound seizures of cocaine are not infrequent, the State Bureau of Narcotic Enforcement employs a mere 130 special agents to investigate these offenses, just 30 more agents then a distant 20 years ago. In comparison, the California Highway Patrol employs some 5000 officers to protect our state highways. Twenty years ago, an agent could testify at several preliminary hearings in one day. Today, just one preliminary hearing may take several days. Our agents are spending more time in court and less time on the street.

On the positive side, the California Bureau of Narcotic Enforcement is utilizing its manpower in a more effective manner. Today, the plan calls for working together, team work. The Federal, state, and local law enforcement agencies are joining forces to combat the drug problem. As I stated previously, the illicit manufacture of drugs has skyrocketed. Many of the illicit laboratories seized today are so sophisticated that they have the capability of producing a number of controlled substances including designer drugs. The California Bureau of Narcotic Enforcement has joined forces with DEA to work together as laboratory task forces in several areas of the state. They have the necessary safety equipment, a centralized intelligence system, and provide training to local law enforcement throughout California on laboratory investigation and safety.

In order to improve law enforcement's effectiveness in drug enforcement within a county, the California Bureau of Narcotic Enforcement has worked with police chiefs and sheriffs and established ten countywide task forces in California with three additional ones to begin within the immediate future. A typical task force is composed of deputy sheriffs and police officers from the local law enforcement agencies within a county. The task force is the sole drug enforcement unit within the county. Each task force is supervised by a California Bureau of Narcotic Enforcement special agent supervisor. The task force concept creates a centralized countywide intelligence system on substance traffickers and pools investigative equipment. It also creates a statewide network of task forces that can exchange information and informants to infiltrate their communities. The average time an officer remains in drug enforcement before returning to a patrol assignment is two years. The Bureau of Narcotic Enforcement supervisor in the task force provides training to the task force officers. The supervisor generally spends the majority of his law enforcement career in drug enforcement and therefore is an expert in the field. If designer drugs appear in a county, the task force informs the Western State Information Network (WSIN) and other task forces throughout the state. This creates an early warning system in California that a new potentially dangerous drug is on our streets and leads to early control of such substance.

Training is a key to success. The California Department of Justice maintains a training academy in Sacramento. The academy trains state and local law enforcement officers throughout the state. A basic two week narcotic school is offered each month of the year. The school covers

the A to Z aspects of controlled substance enforcement. Almost every local officer that enters a narcotic detail attends this school. A segment of the school includes the subject "designer drugs" and laboratory safety. Another school offered to law enforcement officers provides detailed training on designer drugs, their illicit manufacture, and safety.

Previously I discussed law enforcement's ability to track key chemicals used to manufacture controlled substances. This is accomplished by legally requiring a provider of specified chemicals to report the identity of the recipient, his request, and intended use of the chemical to the California Department of Justice twenty-one days prior to releasing it.

California was the first state and is presently one of the states that requires the reporting of key chemical sales to law enforcement. By requiring the seller to make such a report in California, it has forced clandestine chemists to either leave California to purchase their chemicals or to manufacture them, which in most cases is difficult to do. The chemical reporting requirement truly is a benefit to law enforcement in preventing the clandestine manufacturer from obtaining his necessary chemicals. To be even more effective, I believe that the federal government should track these chemicals from the time they are manufactured (usually outside of our state), to the wholesalers throughout the country, to the retailers, and to their ultimate consumers. Only then will we have absolute control of these vital chemicals.

Generally when a new designer drug appears on the street, it is uncontrolled. Law enforcement's hands are tied. The California Attorney General, John Van De Kamp has the authority under 11055(e)(3) of the Uniformed Controlled Substances Act to add PCP analogs onto the list of controlled substances on a temporary basis; however, first notice must be made and a hearing must be held. This procedure, although never used, has been determined to be a slow process. A process must be found to give law enforcement the authority to arrest individuals and seize their designer drug when it first appears on the street.

Law enforcement in California has several other concerns:

First, while doctors and scientists here at this conference discuss working with rhesus monkeys, rats, and cats as guinea pigs toward understanding the effects of designer drugs, law enforcement personnel enter these clandestine laboratory sites and expose themselves to these fumes, chemicals, and other paraphernalia in the course of dismantling and processing the laboratory for subsequent evidence in court. These officers themselves appear to be the guinea pigs. Law enforcement is just beginning to recognize the dangers associated with exposure to these laboratories. Breathing devices and disposable clothing are just beginning to appear. The clothing and breathing devices required must not hinder officers from having the ability to defend themselves when entering these illicit laboratories. Attorney General John Van De Kamp is presently preparing a comprehensive laboratory safety program which will provide medical examinations for his drug agents on an annual basis, and specialized equipment and clothing for illicit laboratory entries.

Another concern is the disposal of the hazardous waste that is generated from these laboratories. The removal of this waste can only be performed by businesses with the proper federal and state licenses. As a result, the

average cost for removing hazardous waste is between 4 to 6 thousand dollars. Costs can run significantly higher. These costs are preventing some law enforcement agencies from aggressively investigating laboratories.

California Assembly Bill 2692 sponsored by Attorney General Van De Kamp and authored by Assemblyman Condit is right on point. The bill enjoys the support of over 100 co-author assemblymen and senators. The bill provides an additional 30 plus state drug enforcement agents, funds for local disposal of hazardous waste, funds for the procurement of laboratory safety equipment that can be loaned out to local law enforcement, funds for expenses incurred by local law enforcement's investigations of laboratories, funds for prosecution of offenders, and funds for prevention literature.

In conclusion, I would like to compliment DEA for presenting this conference. It aligns itself with what I have touched upon today, i.e., working together. With the tremendous amount of heroin and cocaine in this country, we all know that we have a long way to go before we can consider ourselves successful in our efforts to interdict narcotics destined to our citizens. If we become successful in preventing the importation of narcotics into California, will designer drugs flourish? Are we ready when they do? By working together, identifying the tasks ahead, and working toward fulfilling those tasks, I believe that we can effectively combat this potentially explosive problem.

[1]*Editor's Note: N-ethylamphetamine was controlled in Schedule I of the Federal Controlled Substances Act effective January 7, 1982.*

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Legal Aspects

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LEGAL ASPECTS OF CONTROLLED SUBSTANCE ANALOGS
INTRODUCTORY REMARKS

James I.K. Knapp

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I. Controlled Substance Analogs Have Become A Significant Law Enforcement Problem.

A. DuPont chemist Michael Hovey summarized the law enforcement situation when he wrote to his buyer:

"Another point to keep in mind is that I can easily prepare new, unregulated, and completely legal designer drugs by just altering the structures of the fentanyls a bit. The only problem is that we have no way of knowing how potent they are until someone uses them. Perhaps in future deals, I can supply you with new, legal fentanyls and you can get them tested. If one turns up good and potent, we have a true gold mine on our hands because it will be abolutely legal to sell and use it. Keep it in mind".

B. Under the present version of the Controlled Substances Act, unlawful activity is tied to the descriptions of the substances listed in Schedules I and II.

1. Thus, if a particular substance is not included in the existing schedules, it is not illegal to create or distribute the substance without complying with the Act's registration and other requirements, despite the potential for abuse.

2. Including new substances within the statutory schedules is a time-consuming process.

a. The scheduling of a new controlled substance must be accomplished through the rule-making procedure on the record after a hearing, as required by the Administrative Procedure Act [18 U.S.C. §811(a)].

b. However, under section 508 of the Comprehensive Crime Control Act of 1984, authority is provided for the emergency scheduling of substances on a temporary basis.

c. While this reduces the potential for abuse to a great extent, it does not eliminate the problem.

1. A significant period may elapse before the DEA learns that a new substance is being manufactured and is subject to abuse.

2. Further time may elapse before a sample can be obtained and chemically identified. (In the case of China White, a heroin substitute, it was over a year before the DEA learned of the substance and managed to secure and identify a sample).

3. The administrative procedures still take time.

C. The Federal Food, Drug and Cosmetic Act does not satisfactorily address the problem of controlled substances analogs, either.

1. Under this Act, it is unlawful to introduce or to deliver for introduction into interstate commerce any new drug, unless an approval of an application filed under Section 355 is effective, or an exemption from the normal approval requirements applies [21 U.S.C. §355(a)].

2. Punishment for a first offense consists of up to a year in prison, and not more than a $1,000 fine.

3. Furthermore, the Food and Drug Administration does not ordinarily channel its regulatory efforts to control the distribution of illicit, addictive drugs of abuse.

II. Drafting the Statutes To Include Controlled Substance Analogs

A. The controlled substance analog phenomenon is extremely complex, and requires a flexible framework that can resolve both the present foreseeable problems and also anticipate future difficulties.

B. The statute which has been passed by the Senate, and awaits House approval allows a two-prong approach to the controlled substance analog problem.

1. The prosecution must show that there is a ***substantial similarity in chemical structure*** between the substance in question, and a Schedule I or II controlled substance. Steve Stone of the DEA will discuss this aspect in greater detail.

2. Or, the prosecution must show there is a substantial similarity in effect between the substance in question, and a Schedule I or II controlled substance. If the effect prong is in issue, it must be shown that the substance was specifically designed to produce such an effect. Brian Layton, an Assistant United States Attorney (AUSA) in Fresno, California, will summarize this provision.

3. The prosecution must satisfy only one prong of this test, although evidence may be presented on both.

C. Establishing that a controlled substance analog should be treated under the criminal statutes can present formidable problems of proof.

1. Where there is substantial similarity in chemical structure between the controlled substance analog and a controlled substance, the evidence regarding the chemical similarity may be so difficult to grasp that

evidence as to the drug's effect may be helpful in enabling the jury to find that a violation has occurred.

2. Furthermore, given the ingenuity of scientists and rapid technological advances, it may some day be possible to produce a substance which mimics the effects of controlled substances, but is chemically very different.

3. The difficulty facing the drafters was to resolve both problems of proof to cover the myriad of ingenious loopholes that clever chemists might develop.

D. The drafters were also confronted with the problem of combining the disparate statutory schemes of the Controlled Substances Act and the Federal Food, Drug and Cosmetic Act.

1. The Controlled Substances Act combats the illicit drug industry while placing the necessary controls on legitimate industry to prevent the diversion of drugs into illicit channels.

2. The Federal Food, Drug and Cosmetic Act protects the public in its use of drugs which are generally sold or developed for legitimate purposes.

E. Since the controlled substance analog problem is essentially akin to illicit drug dealing, it was determined that the proposed provisions belonged in the statutory scheme of the Controlled Substances Act. Aspects of the Federal Food, Drug and Cosmetic Act have been retained to protect legitimate scientific research.

III. In Drafting This Legislation, Particular Attention Was Also Given To Protecting The Interest Of Legitimate Scientific Researchers.

A. The bill relates only to substances which are substantially similar in chemical structure to the controlled substances in Schedules I and II, and it proscribes the manufacture with intent to distribute, the distribution, and the possession of these substances only if the activity is knowing or intentional.

1. All or part of the particular batch must be intended for human consumption, so a laboratory chemist experimenting with molecules to develop a new industrial chemical could not be affected.

2. Even if the chemist is experimenting with the intent eventually to produce a drug for human consumption, his early stage research is not affected as long as the actual batch of substances involved, or a part of such batch is not intended for human consumption.

B. While the bill could affect the development of a controlled substance analog for medical use at the point of possession, manufacture, or distribution of the actual substances intended for human consumption, protections are there.

1. Activity regarding legitimate new drugs is protected by the bill's exemption for manufacturing, possession, or distribution of a substance in conformance with the new-drug approval provision of the Federal Food, Drug and Cosmetic Act.

2. Early stage research activity is protected by reference to the exemption from the new-drug approval requirement for investigational use provided in 21 U.S.C. §355.

IV. The California Statute

A. The state of California has amended its drug laws to deal with the problem of certain synthetic drugs which have appeared in that state in recent years.

B. The statute explicitly lists the chemical compounds it proscribes.

1. While this includes the synthetic narcotics which have been developed, it does not provide for the chemical compounds which will probably be developed in the future by enterprising chemists.

2. This explicit listing of proscribed substances contrasts with the flexibile two-pronged approach in the federal statute, which will permit the coverage of controlled substance analogs yet to be developed.

STATE LEGISLATIVE RESPONSES TO CONTROLLED SUBSTANCE ANALOGS

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California is one of the states which has passed a law to deal with the continuing designer drug problem. I will be discussing what we did and how we got there. I will also be touching on the approaches several other states - particularly New York, Oklahoma and Florida - are looking at or have already taken.

Our office first began discussing the fentanyl problem in the summer of 1984; in late 1984 Attorney General John Van De Kamp - who has a strong interest in preventing drug abuse and controlling drug-related crime- personally directed a bill be drafted and started looking at specific language. The fact that he was personally interested and involved in the process was a key to the ease, cooperation and speed with which the bill ultimately passed. In fact, the bill was a fine example of a cooperative effort among state, local and private people, law enforcement, chemists, administrators, legislators and lawyers.

In early 1985 Attorney General Van De Kamp had established a task force on drug legislation composed of narcotic agents, chemists, and attorneys, and chaired by Special Agent Robert Elsberg, to review legislation introduced by others as well as to preview and draft Department legislation. Assembly Member William Filante, a physician from Marin County, was carrying a bill - AB 2401 - designed to clean up our controlled substances law and - because he had carried legislation for the Department before - the Department was looking for a drug proposal to give the bill more significance. Our task force decided the problem which most needed to be addressed was designer drugs - because so much of the clandestine activity was in California. This was, of course, consistent with the Attorney General's personal interest in the matter.

We considered two basic approaches: adding specific substances to the schedules or using a broader definition. Adding the substances one-by-one had proven ineffective, especially since California's schedules are amended by statute only, not by regulation. We also decided to focus on the fentanyls as the major problem. The chemists on the Task Force drafted language intended to - and which we believe does - cover all possible variants of fentanyl; the lawyers drafted the language of the bill, which the Attorney General personally reviewed and fine-tuned. We did not seriously consider "intent" language such as that being considered at the Federal level. There is some concern about constitutionality, at least as far as California's constitution is interpreted. Also, as a practical matter, the office did not believe such broad language would pass through our Legislature.

As I said, we settled on a bill which

- we believe - covered all possible forms of fentanyl, trying to anticipate future activity in the fentanyl group, without trying to cover every possibility as to every drug. We basically wound up with what we introduced, along with the inclusion of MPPP and PEPAP in Schedule I. We had some debate over where to place the various fentanyls. Sufentanyl and alpha-methylfentanyl were in Schedule I under existing California law. Sufentanyl was ultimately moved to Schedule II to be consistent with federal law and alpha-methylfentanyl was covered by the generic definition of fentanyl. Eventually the fentanyls - alfentanyl, fentanyl and sufentanyl - were moved to Schedule II; acetylfentanyl and the thiophene analog of acetylfentanyl were placed in Schedule I and were added to the list of drugs expressly defined as narcotics.

The designer drug language was placed into A.B. 2401 on May 1, 1985, at the same time as a great deal of state and national publicity (the March 1985 article in *Science 85*; the *New York* magazine article in May 1985 on MDMA (which is *not* covered by the California law); the April 8, 1985, article in *Time*; an April 5, 1985, pair of articles in the *Los Angeles Times* and so on).

Initially all the fentanyls, including acetylfentanyl, were placed in Schedule II. Eventually, after the bill was reviewed by Roberton and Henderson, acetylfentanyl and the thiophene analog of acetylfentanyl were moved to Schedule I on the grounds that any legitimate use of those drugs was unlikely. On June 24, 1985, A.B. 2401 was amended to be made effective upon signature by the governor.

On August 26, 1985, AB 2401 was amended to move acetylfentanyl and the thiophene analog of acetylfentanyl to Schedule I, but also, based on discussions with manufacturers-particularly Janssen and Johnson and Johnson - engaged in research in the fentanyls, to expressly provide that the California Department of Justice could authorize research into that use. MPPP and PEPAP were added to Schedule I to cover two problem variants of meperidine. MPPP and PEPAP were added at the suggestion of Dr. Langston. He provided material to our Legislative Unit and Randy Rossi, the Legislative Advocate for the Attorney General, who personally directed the inclusion of MPPP and PEPAP in AB 2401. The bill sailed through both houses unanimously, and was signed into law and became effective September 27, 1985 (see Stats 1985, ch. 1098, §§1, 1.2, 1.4, 1.5, 8 and 10). In checking with our Bureau of Narcotic Enforcement and District Attorneys in Los Angeles, San Diego, Orange, San Francisco and Alameda counties I have been unable to find any prosecutions under the new provisions to date.

We are still looking at other designer problems. For example, our possession of chemicals with intent to manufacture methamphetamine statute does not cover ephedrine or red phosphorus, which are being used to manufacture methamphetamine.

Other states have taken or are considering action. Nebraska updated its schedules to include the various drugs - including the fentanyls, MPPP, PEPAP, and MDMA - scheduled on an emergency basis by DEA. The law places the drugs in Schedule I and is effective July 17, 1986. Under its constitution Nebraska must make scheduling changes by statute, so it also considered a generic bill similar to the federal "intent" bill, but it died.

Texas has also included MDMA, MPPP and MPTP in its schedules; it will be looking at the federal legislation and trying to target the chemists

involved since it is impossible to list all the variants which could be designed.

Oklahoma passed a law effective July 1, 1985. It defines "synthetic controlled substance" as an uncontrolled substance which produces a like or similar physiological or psychological effect on the human central nervous system and which substance has no current accepted medical use in the United States and has a potential for abuse. The court or any other authority, in determining if a substance is a "synthetic controlled substance" is directed to also consider: 1) any statement by the owner of the substance or anyone in control of it regarding the nature, use or effect of the substance; 2) statements by the owner to the recipient regarding the potential for resale for an inordinate profit; 3) a prior conviction under federal or state law related to what are - under Oklahoma law - controlled dangerous drugs; and 4) the structural proximity of the substance to a controlled substance. There are penalties for possession with intent to distribute, distribution or manufacturing, but not for simple possession. A first offense has a maximum 5 year term and $25,000 fine. A second offense has a 10 year, $100,000 maximum.

Oklahoma has several prosecutions pending under the law. It has a significant lab program in part because Texas passed a tougher lab law driving some of the labs to the north. A bill is pending to reschedule substances, but Oklahoma is not trying to schedule every variant.

Pennsylvania can change its schedules by regulation; it is incorporating the emergency federal changes but only as a precaution. Controlled substance analogs have apparently not been a real problem in Pennsylvania, and no special legislation is planned.

In Florida, scheduling may be done by regulation; that authority was transferred to the state Attorney General in 1985 and broadened to allow the Attorney General to schedule any appropriate substance. The Attorney General, Department of Law Enforcement and Department of Professional Regulation meet monthly to review federal scheduling and scheduling by other states. As soon as a new designer drug is identified, it would be scheduled by regulation. The Legislature itself is also taking care of scheduling the fentanyls and meperidines.

Florida's lab problem is - however- still primarily related to cocaine, amphetamine and methamphetamine.

In New York, the Department of Health has a detailed proposal under consideration. Independently, a bill- Senate 9234 - was introduced on June 3, 1986. The Department proposal would cover designer drugs and give the Commissioner of the Department of Health the power to change the schedules by regulation (as in California, scheduling is currently done only by statute).

The Commissioner could place a drug in Schedule I on an emergency basis where 1) there was a high potential for abuse; 2) there was no accepted medical use; 3) there was a lack of accepted safety; and 4) such scheduling was necessary to prevent an activity or condition constituting a danger to the health of the people {this last is a phrase found elsewhere in New York law}. Emergency scheduling would last for two years unless the Legislature acted sooner.

The manufacture, distribution or sale of designer drugs would be an offense, unless pursuant to a federal NDA application. This would be a Class B felony (which is the same as for possession of a Schedule I substance). A designer drug would be

expressly defined as a substance other than a prescription drug which is not FDA-approved, not a controlled substance and which is produced to have a primary pharmacological effect on the central nervous system which is substantially the same as a sympathomimetic amine, a depressant, an hallucinogen or a narcotic.

The Senate bill introduced on June 3, 1986, is closer to the federal bill and defines a designer drug as any substance other than a controlled substance listed in Schedule I or II or which was specifically designed to produce an effect substantially similar to that of a controlled substance in Schedule I or II. Knowingly and unlawfully possessing any amount of a designer drug would be a Class C felony. Possession with intent to sell, sale, manufacture or synthesis with intent to sell or distribute would be a Class B felony. There would be an exception for legitimate research authorized by the FDA or the state Department of Health and a provision for licensure of people to do research with controlled substance analogs.

The New York legislature has about one month left; something will pass, but what it will be is not yet certain. The Department of Health, the Division of Substance Abuse and the State Police all support legislation, but there are no hard statistics on which to rely. Autopsies have not focused on designer drugs and - as we know - they are hard for labs to identify. Finally, there is some doubt over whether the "substantially similar" language in the proposal will pass constitutional muster; at the same time there is concern, as, we've heard expressed here, that if New York simply schedules identified analogs, chemists will switch to others.

These are some of the approaches which are being tried or which are in place. Frankly, I feel privileged just to have been invited to be here and to participate; I hope the cooperative spirit of this conference will lead to a stronger overall understanding of the nature of the beast, a coordinated approach and-speaking as a lawyer - clear, enforceable legal standards.

Designer Drugs - Experience at the Haight-Ashbury Free Medical Clinic

Darryl S. Inaba, Pharm.D.

Director, Drug Detoxification Project
Haight-Ashbury Free Medical Clinic
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Federal Legislative Initiative

Stephen E. Stone

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Prosecution of Analog Cases

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Manuscripts for these presentations were not available at press time.

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Discussion Groups and Conference Recommendations

After the presentation of formal papers at the Controlled Substance Analog Leadership Conference, the remainder of the meeting was devoted to group discussions which led to recommendations regarding remedies to the analog problem. Conference attendees participated in at least one of four discussion groups which examined the following areas of concern: 1) health risks and epidemiology, 2) identification and detection, 3) law enforcement, and 4) legal aspects.

Mr. Gene Haislip, Deputy Assistant Administrator of DEA's Office of Diversion Control opened this portion of the meeting with an explanation of the philosophy and expectations of the conference. He urged the participants to take particular care in formulating recommendations since they would be the most important output of the conference. He urged that the recommendations should be such that they could provide guidance to those who need it regardless of what level of government, state, federal or international. He further advised that the guidelines should be general and flexible with a wide range of application yet not so vague as to be impossible to implement. With this charge the four committees met to deliberate and develop strategies to deal with the analog problem.

Following the deliberations of the four groups, the recommendations of each committee were presented to all conference participants. A brief discussion of the recommendations followed. Although there were no significant objections to the recommendations as presented a few suggestions from the floor were incorporated into the final versions. The following are the recommendations of the four expert committees regarding remedies to the problems attendant to the manufacture, distribution and use of controlled substance analogs.

RECOMMENDATIONS OF THE COMMITTEE ON HEALTH RISKS AND EPIDEMIOLOGY

1. The National Institute on Drug Abuse (NIDA) should continue to prepare standards for the analytical determination of illicit drugs and the Drug Enforcement Administration should continue to distribute drug standards to forensic laboratories.

2. A central Federal laboratory should be designated to receive samples of suspected controlled substance analogs for the identification of their contents. Results from the analyses of these drugs should be transmitted to the States to be used in establishing priorities for action.

3. Surveillance for controlled substance analog use should be enhanced. This can be partially accomplished by altering the current program for purchasing street samples. In addition, indicators of illicit use of controlled substance analogs may be identified by the Federal Centers for Disease Control and communicated to State health professionals. Local health professionals can be trained to recognize the effects of controlled substance analog use by the presence of these indicators in patients in drug free clinics and methadone treatment centers and report such use to the State authorities.

4. Other mechanisms to improve surveillance should be explored, such as establishing special telephone hotlines for obtaining and reporting information about the use of controlled substance analogs. These hotlines can be used to direct the drug user to an available treatment center.

5. Research on the physical properties and health effects (including abuse liability studies) of controlled substance analogs and identification of their metabolites in biological samples should be promoted. The results of these studies should be communicated to the individual States through existing national organizations, e.g., the National Association of State Alcohol and Drug Abuse Directors, or by other means.

6. As a high priority, the Centers for Disease Control and the Drug Enforcement Administration should continue their working group to develop guidelines on the most effective procedures to protect forensic and law enforcement personnel from the health consequences of exposure to controlled substance analogs. This might entail categorizing, according to their health risks, those controlled substance analogs and chemicals which already have been found in clandestine laboratory break-ins. The final guidelines should be incorporated into the Drug Enforcement Administration training system and should be communicated to other enforcement agencies and to fire departments through existing networks and/or with the help of professional societies.

RECOMMENDATIONS OF THE COMMITTEE ON IDENTIFICATION AND DETECTION

1. The Federal Government should continue to provide reference standards, analytical methodologies and supplemental analysis of controlled substance analogs to state and local authorities.

2. Existing mechanisms such as the Drug Enforcement Administration's publication of Microgram, forensic meetings and professional organizations should be utilized to facilitate the communication of information regarding analogs among forensic laboratories.

3. A nationwide program for the collection, compilation and dissemination of laboratory analysis data should be initiated. This information should be made available to Federal, state and local officials.

4. Research should be promoted and training and monitoring programs established regarding the safe handling of controlled substance analogs and other hazardous substances by forensic and law enforcement personnel.

5. The development of analytical methodologies for the identification and detection of new drugs in solid samples and biological fluids should be strongly supported.

RECOMMENDATIONS OF THE COMMITTEE ON LAW ENFORCEMENT

1. The increasing number of illegal laboratories seized throughout the United States, and the known hazards for both short-term and long-term adverse health consequences attendant to the seizure of these laboratories, has underscored the need for adequate safety equipment designed specifically for law enforcement personnel.

It is recommended that the Drug Enforcement Administration develop a model, state-of-the-art safety equipment kit for law enforcement personnel. Once developed, information concerning the components of this kit should be widely disseminated to all other Federal, state and local law enforcement agencies.

2. Just as clandestine laboratories pose a unique threat to the safety of law enforcement personnel, they also have significant environmental consequences. Large quantities of potentially toxic chemicals as well as controlled substances are found at these sites. The problem of safe disposal of these chemicals is compounded by varying toxic waste disposal requirements imposed by the United States Environmental Protection Agency (EPA) and state EPA offices.

It is recommended that dialogue with the United States EPA be continued with the objective of developing uniform national guidelines for the disposal of these substances.

3. Recognizing the inadequacies of present laws in dealing with the rising problem of controlled substances analogs, it is recommended that the law enforcement community vigorously support the enactment of the Controlled Substance Analogs Enforcement Act of 1985.

4. Because of the novelty of the controlled substance analog problem and the lack of information available to the law enforcement community, there is a varying awareness of this phenomenon. Some law enforcement agencies have substantial experience and information, whereas others have little. In some regions of the United States, this problem may be aggravated by the failure to screen for controlled substance analogs.

It is recommended that the Drug Enforcement Administration take the lead in compiling, publishing and disseminating information relating to the controlled substance analog problem to all members of the law enforcement and forensic science communities.

5. The controlled substance analog phenomenon is just one aspect of the overall drug problem in the United States. As such, it competes for resources already dedicated to other law enforcement problems. If policy makers believe that law enforcement activities represent an effective method to control this problem, then it will be necessary to devote additional resources in proportion to the problem.

RECOMMENDATIONS OF THE COMMITTEE ON LEGAL ASPECTS

1. The United States Congress should promptly pass the Controlled Substance Analog Enforcement Act of 1985 introduced as Senate Bill 1437.

2. States should promptly enact laws similar to Senate Bill 1437 which are adequate to cover all types of controlled substance analogs and which provide for comparably severe penalties. Further, the ongoing updating of the Uniform Controlled Substances Act should include a model controlled substance analog law.

3. In addition to the enactment of Senate Bill 1437, the Federal Government should continue to schedule the new controlled substance analogs as they are discovered and identified. Further, states should, within the framework of their constitutions, use general administrative scheduling, including the power to follow Federal emergency scheduling for the controlled substance analogs.

4. All jurisdictions, including the Federal Government, should enact legislation to make it clear that the terms "currently accepted medical use in treatment" and "accepted safety for use under medical supervision" mean that the substance is approved for marketing under the Federal Food, Drug and Cosmetic Act.

5. The new proposed United Nations Convention on Narcotics should address the problem of controlled substance analogs and all countries should cooperate in the extradition of the manufacturers and distributors of controlled substance analogs and in the provision of evidence for their trial through such instruments as mutual legal assistance treaties.

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ADDENDUM

On October 27, 1986, President Reagan signed the Anti-Drug Abuse Act of 1986 (Public Law 99-570). Subtitle E of Title I of this law is known as the Controlled Substance Analogue Enforcement Act of 1986. This law amends the Controlled Substances Act by providing that controlled substance analogs when used for human consumption outside of the new drug provisions of the Federal Food, Drug and Cosmetic Act be treated as Schedule I substances.

With the passage of this bill as recommended by those participating in the Controlled Substance Analog Leadership Conference, individuals can no longer manufacture and distribute controlled substance analogs without fear of prosecution. Hopefully the new law will act as a deterrent and diminish the threat from the spread of these dangerous substances.

Subtitle E

Controlled Substance Analogue Enforcement Act of 1986

Sec. 1201. Short Title.

This subtitle may be cited as the "Controlled Substance Analogue Enforcement Act of 1986".

Sec. 1202. Treatment of Controlled Substance Analogues.

Part B of the Controlled Substances Act is amended by adding at the end the following new section:

TREATMENT OF CONTROLLED SUBSTANCE ANALOGUES

"Sec. 203. A controlled substance analogue shall, to the extent intended for human consumption, be treated, for the purposes of this title and title III as a controlled substance in Schedule I."

Sec. 1203. Definition.

Section 102 of the Controlled Substances Act (21 U.S.C. 802) is amended by adding at the end thereof the following:

"(32)(A) Except as provided in subparagraph (B), the term 'controlled substance analogue' means a substance-

"(i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in Schedule I or II;

"(ii) which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than

the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in Schedule I or II; or

"(iii) with respect to a particular person, which such person represents or intends to have a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in Schedule I or II.

"(B) Such term does not include-

"(i) a controlled substance;

"(ii) any substance for which there is an approved new drug application;

"(iii) with respect to a particular person any substance, if an exemption is in effect for investigational use, for that person, under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) to the extent conduct with respect to such substance is pursuant to such exemption; or

"(iv) any substance to the extent not intended for human consumption before such an exemption takes effect with respect to that substance."

Sec. 1204. Clerical Amendment.

The table of contents of the Comprehensive Drug Abuse Prevention and Control Act of 1970 is amended by inserting after the item relating to section 202 the following new item:

"Sec. 203. Treatment of controlled substance analogues."

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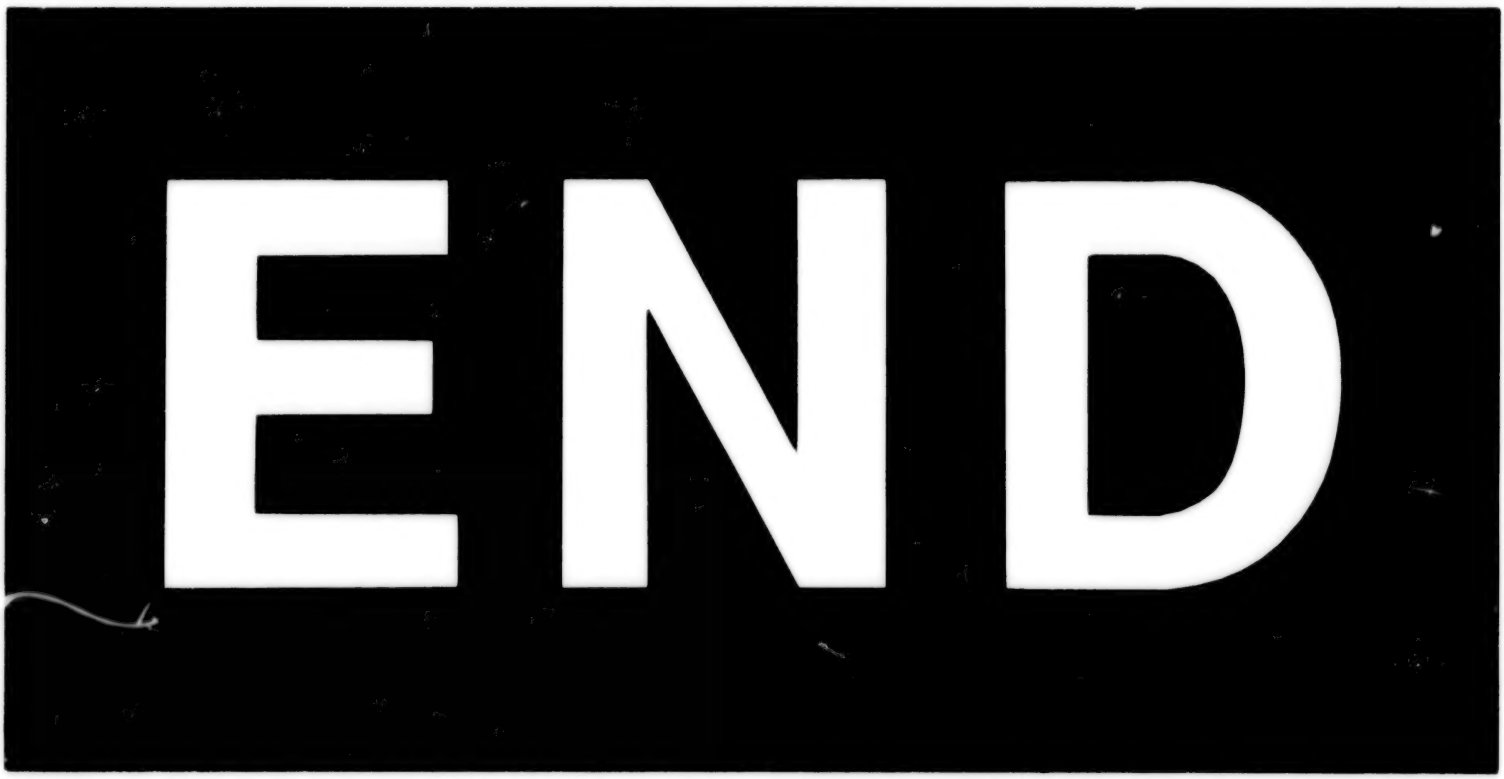

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